ORIGINAL ARTICLE

How do inflammatory marker dynamics shift with acute calculous cholecystitis severity?

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ABSTRACT

BACKGROUND: Gallstones can lead to complications such as cholecystitis, gallbladder gangrene, perforation, and related sepsis. This study aims to evaluate how C-reactive protein (CRP) and immune cells change in patients with acute calculous cholecystitis based on the severity of the disease.

METHODS: Patients with acute calculous cholecystitis were categorized into three main groups—mild, moderate, and severe—according to the Tokyo guidelines. CRP, neutrophil counts, lymphocyte counts, helper T cells, cytotoxic T lymphocytes, and human leukocyte antigen-DR (HLA-DR) expression on $CD14^+$ monocytes were measured using flow cytometry at the time of hospitalization for all patients. Differences between the groups were analyzed.

RESULTS: No significant differences were observed in lymphocyte count, $CD3^+$, $CD4^+$, $CD8^+$ cells, or $CD4^+/CD8^+$ ratios between the groups. However, lymphocyte count and $CD3^+$ cells showed a decreasing trend, while the CD4/CD8 ratio increased with disease severity, though these changes were not statistically significant. Neutrophil count, neutrophil/lymphocyte ratio (NLR), CRP levels, and HLA-DR expression on $CD14^+$ monocytes significantly increased with cholecystitis severity. HLA-DR had a sensitivity of 66.7% and specificity of 92.9%, CRP had a sensitivity of 78.6% and specificity of 81.00%, and NLR had a sensitivity of 85.7% and specificity of 76.2% for predicting severe cholecystitis.

CONCLUSION: Evaluating CRP, NLR, lymphocyte count, total $CD3^+$ cells, CD4/CD8 ratio, and HLA-DR expression on monocytes at hospital admission can provide clinicians with valuable prognostic information about acute calculous cholecystitis severity.

Keywords: Acute cholecystitis; human leukocyte antigen-DR (HLA-DR); lymphocyte; monocyte; sepsis.

INTRODUCTION

Gallbladder diseases represent a significant global health concern. Approximately 20% of the general population has symptomatic gallstones, and acute calculous cholecystitis (ACC) develops in 20% of these patients.[1] If untreated, ACC, driven by biochemical and bacterial inflammatory processes, can lead to life-threatening complications.

Acute calculous cholecystitis typically occurs when a gallstone obstructs the cystic duct, resulting in inflammation. Gallstones are responsible for 95% of cases, while tumors account for about 1%. Secondary bacterial infection often follows. Although removing the obstruction usually resolves symptoms, persistent blockage can lead to complications such as gangrene, perforation, and sepsis in 10% of cases.[2] Diagnosing ACC requires a comprehensive assessment, including patient history, physical examination, laboratory findings, and imaging

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results. No single test can definitively confirm or exclude the diagnosis. The Tokyo guidelines classify the severity of ACC based on physical examination, laboratory tests, disease duration, organ function, and imaging.[3,4] However, no objective test currently exists to predict the clinical course of ACC.

Flow cytometry, a technique used in diagnosing various diseases and conducting biological studies, allows for the analysis of cell-related molecules, including cell morphology, surface and intracellular protein expression, gene expression, and cellular physiology. It enables the rapid analysis of large numbers of cells using fluorescence and light scattering signals.[5] While some studies have employed flow cytometry to analyze lymphocyte subgroups in patients with acute appendicitis and acute pancreatitis by observing changes in blood cell populations typical of infectious diseases, no literature exists on the use of flow cytometric lymphocyte subgroup analysis to assess the severity or treatment options for ACC.[6,7]

The aim of this study is to determine the role of inflammatory markers and immune system cells in predicting the disease course, identify changes in immune cells based on the severity of ACC, and understand the immunological status of severe ACC patients to inform potential treatments targeting the immune system.

MATERIALS AND METHODS

Patients Selection and Ethical Statement

Patients hospitalized with ACC between September 2019 and June 2020 were prospectively enrolled in the study following approval from University of Health Sciences Istanbul Training and Research Hospital Clinical Research Ethics (date: 01.02.2019, decision no: 1664). To determine the required sample size, a power analysis was performed, which calculated that at least 14 volunteers should be included in each group to achieve 80% power with a 0.47 effect size.[8] Patients were sequentially included in the study based on their order of admission, and recruitment for each group was concluded once 14 patients were enrolled. The control group consisted of healthy volunteers without any known diseases or gallstones. All participants provided written informed consent after receiving a full explanation of the study. The study included adults aged 18-85 with acute gallstone-induced gallbladder inflammation but excluded individuals with the following conditions: gallbladder inflammation without stones, concurrent pancreatic inflammation, diabetes, a history of cancer, pregnancy, age below 18 or above 85, immune system deficiencies, or unwillingness to participate. At the time of hospitalization, blood inflammatory parameters were evaluated alongside hepatobiliary ultrasonography or abdominal magnetic resonance imaging (MRI). Patients were categorized into three groups—mild, moderate, and severe ACC—based on the Tokyo guidelines.

Preparation of Blood Sample

A 10-milliliter blood sample was collected in a heparin-coated vial from eligible participants during their hospital stay. From this sample, 100 microliters of blood were placed into two separate tubes: no antibodies were added to the first tube, while the second tube received the following primary antibodies: CD3 labeled with APC-Cy7 (Biolegend, USA, cat no: 344818), CD4 labeled with PerCP/Cyanine5.5 (Biolegend, USA, cat no: 357413), CD8 labeled with PE/Cyanine7 (Biolegend, USA, cat no: 344711), CD45 labeled with V500-C (BD Company, USA, cat no: BD 655873), CD14 labeled with APC (BD Company, USA, cat no: BD 345787), and human leukocyte antigen-DR (HLA-DR) labeled with V450 (BD Company, USA, cat no: BD 561359) at dilutions specified by the manufacturers. Flow cytometric analysis was performed within 24 hours of blood collection.

The age, gender, neutrophil and lymphocyte counts, C-reactive protein (CRP) levels, and flow cytometry results of the patients at the time of hospitalization were recorded and compared between the control group and the ACC subgroups.

Statistical Analysis

Power analysis was conducted using the G*Power software (version 3.1.9.7) with an Analysis of Variance (ANOVA) test. The percentage ratios of lymphocyte subtypes were calculated and categorized based on the study groups. Normally distributed data were presented as mean ± standard deviation, while non-normally distributed data were presented as median (minimum-maximum). Each parameter was analyzed using the Statistical Package for the Social Sciences (SPSS) software for Windows (v22.0; IBM, Armonk, NY, USA) to identify significant differences between groups. The distribution of variables was evaluated using the Kolmogorov-Smirnov test. For independent, normally distributed data, variance uniformity was assessed with Levene's test. Group comparisons were conducted using a One-Way ANOVA for independent, normally distributed, and uniform data, while the Kruskal-Wallis test was used for non-normally distributed independent data. When significant differences emerged in the One-Way ANOVA test, the Tukey test was applied for post hoc analysis. For non-normal distributions, Dunn's test was used following the Kruskal-Wallis test. Chi-square tests were conducted for independent qualitative data analysis. Correlation analysis utilized Spearman's correlation coefficient for non-normal distributions and Pearson's correlation coefficient for normal distributions, depending on disease severity. Correlations were interpreted as follows: 0.00-0.19 (negligible), 0.20-0.39 (weak), 0.40-0.59 (moderate), 0.60-0.79 (strong), and 0.80-1.0 (very strong). To assess the sensitivity and specificity of the thresholds for CRP, neutrophil-to-lymphocyte ratio (NLR), and HLA-DR percentage in predicting severe cases, receiver operating characteristic (ROC) curve analysis was performed.

RESULTS

The study initially enrolled 42 individuals diagnosed with acute biliary gallbladder inflammation. However, one participant withdrew consent, three were newly diagnosed with diabetes or cancer, and seven tested positive for Coronavirus Disease 2019 (COVID-19), resulting in their exclusion. To maintain the sample size, 11 additional eligible participants were recruited in the order of hospital admission (Fig. 1). The average age of participants was 49.02±16.34 years, with an 11/17 female-to-male ratio among the 42 ACC patients and 14 healthy volunteers. Significant differences in age, neutrophil counts, and neutrophil-to-lymphocyte ratio were observed among the groups (Table 1). Further analysis revealed significant age differences between the control group and the severe inflammation groups (p=0.004) as well as between the mild and severe inflammation groups (p=0.005). Regarding neutrophil counts, significant differences were found between:

- Control and mild inflammation groups (p=0.011),
- Control and moderate inflammation groups (p<0.001),
- Control and severe inflammation groups (p<0.001),
- Mild and moderate inflammation groups (p=0.016), and
- Mild and severe inflammation groups (p<0.001).

For NLR, subgroup analysis revealed significant differences between:

- Control and mild inflammation groups (p=0.002),
- Control and moderate inflammation groups (p<0.000),
- Control and severe inflammation groups (p<0.000), and
- Mild and severe inflammation groups (p<0.011).

Additionally, leukocytes exhibited a very strong positive correlation, NLR a strong positive correlation, lymphocytes a weak negative correlation, and age a moderate positive correlation with disease severity (Table 1).

The CRP values showed significant differences between the groups (p<0.001). Subgroup analyses revealed that this statistical difference was due to differences between the control group and the mild, moderate, and severe groups (p=0.022, p<0.001, p<0.001, respectively), as well as between the mild group and the moderate and severe groups (p=0.010, p<0.001, respectively). Additionally, CRP levels exhibited a very strong positive correlation with disease severity (Table 1).

As the severity of gallbladder inflammation escalated across the groups, a considerable decline in HLA-DR levels on $CD14^{+}$ monocytes was observed, measured using flow cytometer. This decline demonstrated a moderately inverse relationship. Further examination revealed that the significant variation in HLA-DR levels was primarily due to differences between the control and severe groups (p=0.000) and between the mild and severe groups (p=0.008), as illustrated in Table 2.

The cut-off values, sensitivity, and specificity of CRP, NLR,

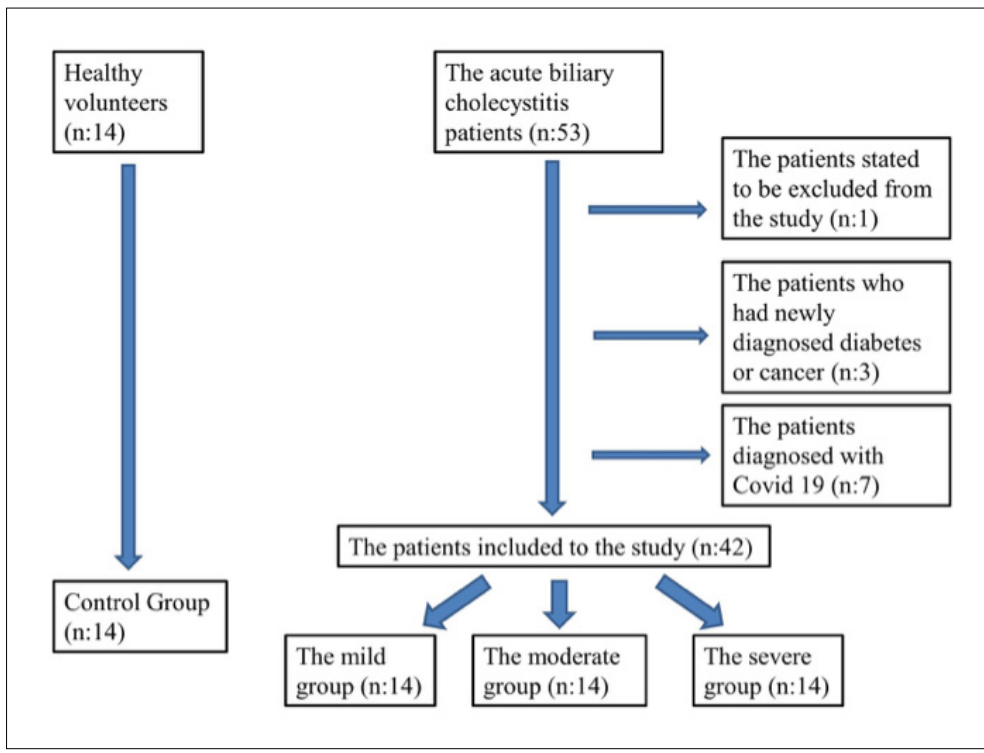

Figure 1. Flowchart of patient inclusion in the study.

Table 1. Demographic data and distribution of leukocytes and lymphocytes of participants based on disease severity

	Group 1 (Control) (n=14)	Group 2 (Mild Cholecystitis) (n=14)	Group 3 (Moderate Cholecystitis) (n=14)	Group 4 (Severe Cholecystitis) (n=14)	p value	Correlation (r, p)
Age (Years) (Median, min-max)	37.0 (29.0-62.0)	40.5 (24.0-63.0)	53.0 (53.0-83.0)	55.0 (26.0-88.0)	0.001[a]	r=0.521 p<0.001
Gender Female (n, %)	5 (35.71%)	5 (35.71%)	5 (35.71%)	6 (42.85%)	0.960[b]	NA
Gender Male (n, %)	9 (64.29%)	9 (64.29%)	9 (64.29%)	8 (57.15%)		
Neutrophil (10^9/L) (Median, min-max)	4.35 (2.76-8.05)	10.43 (9.00-20.74)	17.10 (15.60-22.30)	20.50 (16.10-23.33)	<0.001[a]	r=0.909 p<0.001
Lymphocyte (10^9/L) (Median, min-max)	2.37 (1.20-3.95)	2.05 (1.16-3.00)	2.07 (1.26-2.90)	1.85 (0.50-5.20)	0.079[a]	r=-0.328 p=0.014
NLR (Median, min-max)	1.73 (1.14-4.83)	5.05 (3.00-16.46)	8.66 (6.50-15.67)	9.52 (4.00-45.00)	<0.001[a]	r=0.620 p<0.001
CRP (mg/L) (Median, min-max)	6.50 (2.00-23.00)	46.00 (6.00-103.00)	102.00 (54.00-219.00)	163.00 (38.00-261.00)	<0.001[a]	r=0.809 p<0.001

[a]Kruskal-Wallis Test; [b]Chi-square test. SD: Standard Deviation; NA: Not Applicable; NLR: Neutrophil/Lymphocyte Ratio; CRP: C-Reactive Protein.

Table 2. Distribution of flow cytometry results by groups

Parameter	Group 1 (Control) (n=14)	Group 2 (Mild Cholecystitis) (n=14)	Group 3 (Moderate Cholecystitis) (n=14)	Group 4 (Severe Cholecystitis) (n=14)	p value	Correlation (r, p)
$CD3^+$ (%) (Median, min-max)	72.28 (55.0-79.0)	75.85 (50.50-84.80)	70.10 (40.90-83.60)	76.50 (24.00-90.00)	0.621[a]	r=0.086 p=0.529
$CD4^+$ (%) (Median, min-max)	56.40 (36.0-67.0)	59.45 (50.00-75.00)	57.50 (49.00-72.00)	69.40 (22.00-82.00)	0.245[a]	r=0.270 p=0.044
$CD8^+$ (%) (Median, min-max)	35.79 (25.00-52.00)	33.25 (23.00-55.00)	37.50 (21.00-58.00)	29.00 (15.00-73.00)	0.621[a]	r=-0.109 p=0.423
$CD4^+$-$CD8^+$ (%) (Median, min-max)	1.25 (0.10-3.21)	1.35 (0.48-3.20)	1.80 (0.40-7.04)	1.10 (0.00-4.00)	0.276[a]	r=-0.013 p=0.922
$CD4^+/CD8^+$ Ratio (Median, min-max)	1.58 (0.68-2.64)	1.67 (0.72-3.28)	1.57 (0.84-3.17)	2.33 (0.30-5.40)	0.463[a]	r=0.182 p=0.180
$CD14^+$/HLA-DR^+ (%) (Mean±SD)	91.06±5.39	88.44±7.50	83.84±7.45	79.18±8.39	0.000[b]	r=-0.539 p=0.000

[a]Kruskal-Wallis Test; [b]One-Way Analysis of Variance (ANOVA) test. SD: Standard Deviation.

and HLA-DR levels for predicting moderate and severe ACC are presented in Table 3. Dot-plot images of HLA-DR ratios for the groups are provided as supplementary material.

DISCUSSION

Acute calculous cholecystitis is a serious complication of gallstones, with a mortality rate of approximately 3%, which may

Table 3. Cut-off values of C-reactive protein (CRP), neutrophil-to-lymphocyte ratio (NLR), and human leukocyte antigen - DR isotype (HLA-DR) to predict moderate and severe acute calculous cholecystitis, along with their sensitivity and specificity based on receiver operating characteristic (ROC) curve analysis

		Sensitivity	Specificity
CRP	Moderate (>77.50 mg/L)	85.7%	92.9%
	Severe (>101.00 mg/L)	78.6%	81.00%
NLR	Moderate (>5.37)	96.4%	82.1%
	Severe (>8.48)	85.7%	76.2%
HLA-DR	Moderate (>84.70%)	64.3%	85.7%
	Severe (>86.8%)	66.7%	92.9%

CRP: C-Reactive Protein; NLR: Neutrophil-to-Lymphocyte Ratio.

increase with age and the presence of comorbidities. Delays in appropriate treatment can lead to severe complications. The widely accepted primary intervention for acute gallbladder inflammation is early surgical removal of the gallbladder using minimally invasive techniques, combined with appropriate fluid, electrolyte, and antibiotic therapy.[9] Various predictive markers are utilized to determine the prognosis of patients with ACC.[10,11]

Nevertheless, these clinical measurements have certain limitations. For instance, factors unrelated to inflammation, such as a patient's age or sex, can influence these biological indicators.[10] One of the most commonly used markers is C-reactive protein. Studies have demonstrated a relationship between elevated CRP levels and severe ACC, suggesting that the cut-off CRP levels for moderate and severe disease are 70.65 mg/L and 198.95 mg/L, respectively, with high sensitivity and specificity rates.[11] Similarly, researchers have suggested that NLR can be applied to identify acute gallbladder inflammation, as it is already used to detect various other medical conditions.[12] The literature has shown that complicated ACC cases exhibit higher NLR values compared to non-complicated cases, supporting its potential utility in assessing the severity of ACC.[13] In our study, we found that CRP and NLR levels increased with disease severity and demonstrated high sensitivity and specificity for predicting disease severity.

Immunosuppression is often marked by reduced HLA-DR expression, reflecting inactive monocytes and decreased circulating lymphocytes. Scientists have developed various biological markers to identify patients with sepsis-related monocyte dysfunction. Lower HLA-DR expression has been shown to correlate with higher mortality rates and increased hospital-acquired infections in septic patients.[14,15] Acute pancreatic inflammation is a frequent complication in patients with gallstones, and although limited, some studies have explored immunophenotyping using flow cytometry in these patients. A study reported that in cases of infectious complications in acute pancreatitis patients, circulating lymphocyte counts were decreased, and HLA-DR expression in $CD14^+$ monocytes was reduced compared to patients without infectious complications, consistent with the phenomenon of immune dysfunction. Additionally, it has been reported that the percentage of $CD14^+$ monocytes expressing HLA-DR at the onset of acute pancreatic inflammation independently predicts infectious complications. Numerous studies have demonstrated that lower HLA-DR expression strongly correlates with poor outcomes in patients with acute pancreatic inflammation.[16,17] Our research similarly revealed a significant decrease in monocyte HLA-DR expression as the severity of gallbladder inflammation increased.

During sepsis, the death of $CD4^+$ T cells significantly impacts antigen-specific effector $CD4^+$ T cells, leading to impaired adaptive immune functions. Even when $CD4^+$ T cell counts are stable, their responses may be altered due to sepsis-induced immunosuppression. Studies on lymphocyte counts in patients with severe inflammation and sepsis report varied findings. A review highlighted that changes in $CD4^+$ T cell numbers and function influence the magnitude and effectiveness of the immune response during sepsis.[18] One study found that $CD3^+$ T cells and $CD3^+$-$CD4^+$ T cells increased with the severity of pancreatic inflammation, while $CD3^+$-$CD8^+$ T cells decreased.[19] Yang et al.[20] reported a significant reduction in $CD4^+$ T cells in severe acute pancreatitis, which correlated with an increase in complications. Another study found that $CD4^+$ T cells and the $CD4^+/CD8^+$ ratio decreased

more significantly in severe pancreatic inflammation than in mild cases, with no notable difference in $CD8^+$ cell counts.[21] However, our study on gallbladder inflammation found no significant differences in $CD3^+$, $CD4^+$, $CD8^+$ cell counts, or the $CD4^+/CD8^+$ ratio compared to controls. While hemogram parameters showed no difference in total lymphocyte counts, a decline in lymphocyte numbers was observed as the disease severity progressed.

Our study's limitations include the limited examination of T cell subtypes and the absence of an asymptomatic gallstone patient group.

CONCLUSION

Our study is the first in the literature to examine T cell subtypes and HLA-DR ratios on monocytes in patients with ACC. Our findings demonstrate a reduction in HLA-DR expression and CRP levels correlating with disease severity. Specifically, HLA-DR expression below 86.8% on monocytes and CRP values above 101.00 mg/L were indicative of severe disease. Although not statistically significant, increasing disease severity was associated with decreases in total lymphocyte counts and the total CD3+ cell percentage. Additionally, ACC severity strongly correlated with elevated leukocyte counts. We believe that assessing these parameters at hospital admission can provide clinicians with valuable insights into disease progression. Future studies focusing on additional T cell subtypes will further enrich the existing literature.

Ethics Committee Approval: This study was approved by the University of Health Sciences Istanbul Training and Research Hospital Clinical Research Ethics Committee (Date: 01.02.2019, Decision No: 1664).

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Authorship Contributions: Concept: E.E.; Design: E.E., U.O.İ.; Supervision: E.E., U.O.İ.; Resource: E.E., E.K., U.O.I.; Materials: E.E., A.E.N., M.M.S., E.K., B.O.; Data collection and/or processing: E.E., A.E.N., M.M.S., E.K., B.O.; Analysis and/or interpretation: E.E., U.O.İ.; Literature review: E.E., A.E.N., M.M.S., E.K., B.O.; Writing: E.E., A.E.N., M.M.S., E.K., B.O.; Critical review: U.O.İ.

Conflict of Interest: None declared.

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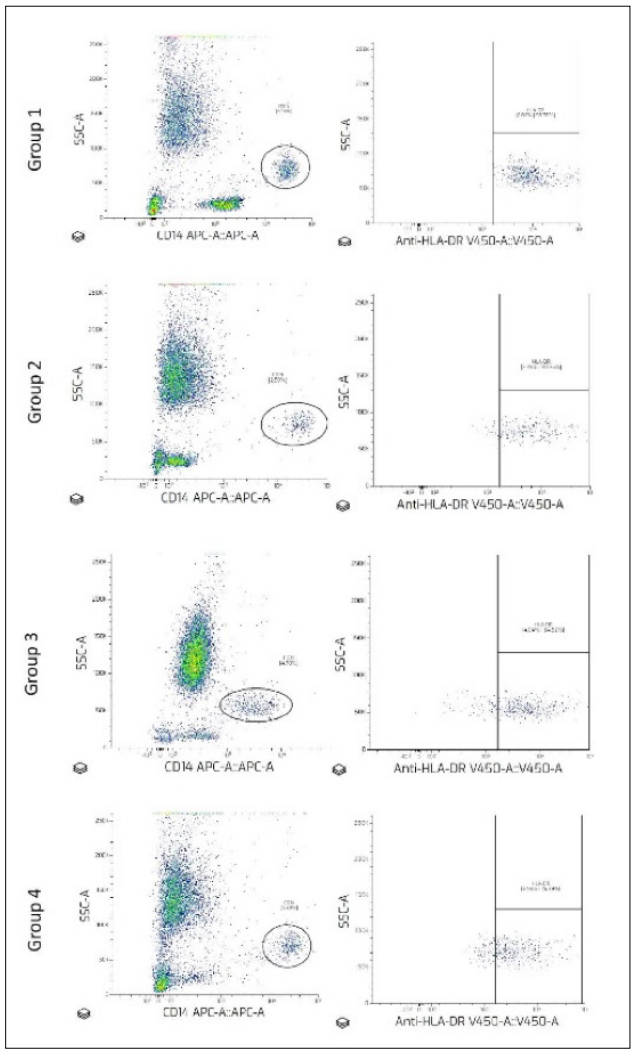

Supplementary Material. Flow cytometric dot-plot cell images showing CD14+/HLA-DR+ (%) for each group.

ORİJİNAL ÇALIŞMA - *ÖZ*

Akut kalküloz kolesistit şiddeti ile enflamatuvar belirteçler nasıl değişir?

AMAÇ: Safra taşları, kolesistit, safra kesesi gangreni, perforasyon ve ilişkili sepsis gibi komplikasyonlara yol açabilir. Bu çalışma, akut kalküloz kolesistit hastalarında hastalığın şiddetine göre CRP ve bağışıklık hücrelerinin nasıl değiştiğini belirlemeyi amaçlamaktadır.
GEREÇ VE YÖNTEM: Akut kalküloz kolesistitli hastalar, Tokyo kılavuzlarına göre hafif, orta ve şiddetli olmak üzere üç ana gruba ayrıldı. Tüm hastalardan hastaneye yatış sırasında CRP, nötrofil, lenfosit, yardımcı T hücreleri, sitotoksik T lenfositleri ve $CD14^+$ monositlerdeki HLA-DR ekspresyonu akım sitometrisi ile ölçüldü ve gruplar arasında farklılık olup olmadığı değerlendirildi.
BULGULAR: Lenfosit sayısı, $CD3^+$, $CD4^+$, $CD8^+$ hücreler ve $CD4^+/CD8^+$ oranı açısından gruplar arasında anlamlı bir fark yoktu. Anlamlı olmasa da, lenfosit sayısı ve $CD3^+$ hücreler azalma eğilimindeyken, CD4/CD8 oranı hastalık şiddeti ile birlikte artma eğilimindeydi. Bununla birlikte, nötrofil sayısı, Nötrofil/Lenfosit Oranı (NLR), CRP ve $CD14^+$ monositlerdeki HLA-DR ekspresyonu kolesistit şiddeti ile anlamlı derecede arttı. HLA-DR, şiddetli kolesistiti öngörmede %66.7 duyarlılık ve %92.9 özgüllüğe, CRP ise %78.6 duyarlılık ve %81.00 özgüllüğe ve NLR %85.7 duyarlılık ve %76.2 özgüllüğe sahiptir.
SONUÇ: CRP, NLR, lenfosit sayısı, toplam $CD3^+$ hücreler, CD4/CD8 oranı ve monositlerde HLA-DR ekspresyonunun hastaneye yatış sırasında değerlendirilmesi, klinisyenlere hastalığın prognozu hakkında değerli bilgiler sağlayabilir.

Anahtar sözcükler: Akut kolesistit; HLA-DR; lenfosit; monosit; sepsis.

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