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A novel approach to distinguish complicated and non-complicated acute cholecystitis

Decision tree method

Afig Gojayev, MD[a,*], Emre Karakaya, MD[a], Murathan Erkent, MD[a], Sait Can Yücebaş, PHD[b], Hüseyin Onur Aydın, MD[a], Lara Kavasoğlu, MD[a], Cem Aydoğan, MD[a], Sedat Yıldırım, MD[a]

Abstract

It is difficult to differentiate between non-complicated acute cholecystitis (NCAC) and complicated acute cholecystitis (CAC) preoperatively, which are two separate pathologies with different management. The aim of this study was to create an algorithm that distinguishes between CAC and NCAC using the decision tree method, which includes simple examinations. In this retrospective study, the patients were divided into 2 groups: CAC (149 patients) and NCAC (885 patients). Parameters such as patient demographic data, American Society of Anesthesiologists (ASA) score, Tokyo grade, comorbidity findings, white blood cell (WBC) count, neutrophil/lymphocyte ratio, C-reactive protein (CRP) level, albumin level, CRP/albumin ratio (CAR), and gallbladder wall thickness (GBWT) were evaluated. In this algorithm, the CRP value became a very important parameter in the distinction between NCAC and CAC. Age was an important predictive factor in patients with CRP levels >57 mg/L, and the critical value for age was 42. After the age factor, the important parameters in the decision tree were WBC and GBWT. In patients with a CRP value of ≤57 mg/L, GBWT is decisive and the critical value is 4.85 mm. Age, neutrophil/lymphocyte ratio, and WBC count were among the other important factors after GBWT. Sex, ASA score, Tokyo grade, comorbidity, CAR, and albumin value did not have an effect on the distinction between NCAC and CAC. In statistical analysis, significant differences were found groups in terms of gender (34.8% vs 51.7% male), ASA score ($P < .001$), Tokyo grade ($P < .001$), comorbidity ($P < .001$), albumin (4 vs 3.4 g/dL), and CAR (2.4 vs 38.4). By means of this algorithm, which includes low-cost examinations, NCAC and CAC distinction can be made easily and quickly within limited possibilities. Preoperative prediction of pathologies that are difficult to manage, such as CAC, can minimize patient morbidity and mortality.

Abbreviations: CAC = complicated acute cholecystitis, CAR = CRP/albumin ratio, CRP = C-reactive protein, GBWT = gallbladder wall thickness, NCAC = non-complicated acute cholecystitis, NLR = neutrophil/lymphocyte ratio, WBC = white blood cell.

Keywords: cholecystitis, decision tree, gangrenous cholecystitis, necrotizing cholecystitis, perforated cholecystitis

1. Introduction

Acute cholecystitis is an inflammatory pathology of the gallbladder and one of the most common emergency surgeries.[1] The gold standard in its treatment is laparoscopic cholecystectomy.[2] Complicated acute cholecystitis (CAC), which can be fatal, such as gangrenous cholecystitis, gallbladder perforation, and emphysematous cholecystitis, develops as a result of disruption of the vascular circulation of the gallbladder wall in 2% to 30% of patients with acute cholecystitis.[2] Patients who develop CAC have longer intensive care unit and hospital stays, and higher morbidity (29%) and mortality (15–50%) rates.[3,4] Preventing of such complications is possible through early diagnosis and intervention.[5] However, this is very difficult to predict, and only 9% of patients can be diagnosed with CAC preoperatively.[6]

In this study, we aimed to create an algorithm to distinguish between CAC and non-complicated acute cholecystitis (NCAC) using the decision tree method with using simple and available parameters such as demographic, laboratory and ultrasonographic findings. With this algorithm, we aimed to distinguish between CAC and NCAC at an early time with greater accuracy even within limited possibilities.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of General Surgery, Baskent University School of Medicine, Ankara, Turkey, [b] Faculty of Engineering, Computer Engineering Department, Canakkale Onsekiz Mart University, Çanakkale, Turkey.

**Correspondence: Afig Gojayev, Department of General Surgery, Baskent University, School of Medicine, Ankara Hospital, Bahçelievler/Ankara, Turkey (e-mail: afiggojayev@gmail.com).*

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2. Material and methods

This study was approved by the Baskent University Faculty of Medicine Clinical Research Ethics Committee (project number: KA22/435). In our study, the data of 1115 patients who underwent surgery for acute calculous cholecystitis in our clinic between January 2011 and March 2022 were evaluated retrospectively.

Patients were divided into 2 groups according to their intraoperative and histopathological findings: CAC (n = 149) and NCAC (n = 885). One hundred forty-nine patients diagnosed with gangrenous, necrotic, perforated and emphysematous cholecystitis clinically, radiologically and histopathologically were included in the CAC group. Patient characteristics and laboratory-ultrasonographic findings were compared between groups. Demographic data (age, sex), American Society of Anesthesiologists (ASA), Tokyo grade, and comorbidity findings (diabetes mellitus [DM], coronary artery disease [CAD], chronic obstructive pulmonary disease [COPD]) were included in the patient characteristics. Laboratory ultrasonography findings included white blood cell (WBC) count, neutrophil lymphocyte ratio (NLR), C-reactive protein (CRP), albumin, CRP/albumin ratio (CAR), and gallbladder wall thickness (GBWT). Eighty-one patients with gallbladder malignancies detected on pathological examination or missing data were excluded from the study (Fig. 1).

2.1. Decision tree method

A decision tree is a machine learning method that forms a tree like structural path to indicate the classification result and determine the affecting variables.[7] The paths of the tree indicate rules as if/else conditions, and together forms a stepwise algorithmic solution of the given problem.[8] A tree is formed by calculating the information gain based on entropy. Entropy, which is an information theory concept, indicates the amount of information contained in a variable. In the case of a classification whose outcome is not known beforehand, it quantifies the effect of variables likely to affect the outcome on this uncertainty. In our case, the uncertainty decision is NCAC and CAC, while there are variables such as CRP, Age, GBWT, NLR, and WBC that affect this uncertainty. By entropy, the possible effect of each variable on this uncertain outcome can be calculated numerically. High entropy means high uncertainty. The variable with lowest entropy will increase the information gain (given in 3rd equation). This variable is interpreted as the variable with the highest impact on the classification decision. Thus it is assigned to the root node. With iterative recursive calculations, the remaining variables are assigned to the other nodes of the tree according to information gain calculation. The following paragraphs explain how entropy and information gain are calculated mathematically.

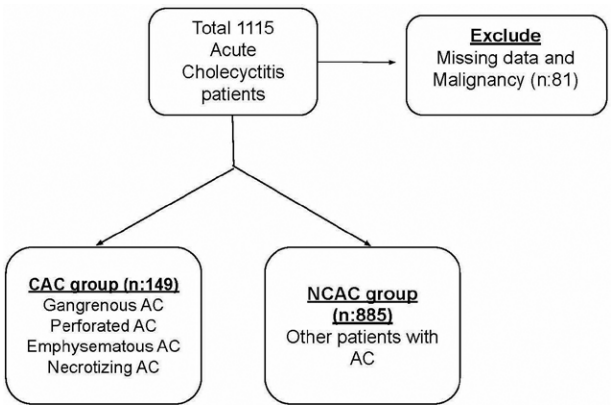

Figure 1. Flowchart of the study population. AC = acute cholecystitis, CAC = complicated acute cholecystitis, NCAC = non-complicated acute cholecystitis.

The information is a logarithmic representation of a given variable and is calculated as follows:

$$Info = -\sum_{i=1}^{m} p_i \log_2 p_i$$

For any attribute that divides the dataset into S sub samples, the entropy value is calculated as follows:

$$Entropy_{Attribute} = \sum_{i=1}^{l} \frac{S_{1i} + \ldots + S_{li}}{S} * Info$$

Then the information gain for a given attribute is the difference between the total information and entropy of the given attribute. This difference was calculated as follows:

$$Information\ Gain_{Attribute} = Info - Entropy\_Attribute$$

In our study, a decision tree with a maximum depth of 15 was used. Each leaf is formed to have at least two samples in it and the minimum sample number for a node to split further is determined to be 4. To prevent the model from overfitting a tenfold cross validation with stratified sampling was used. The area under the curve (AUC) metric was used to test the model's decision performance, and was calculated as 0.885.

2.1.1. Statistical analysis. The study plans were retrospectively reviewed. Categorical variables were expressed as numbers and percentages. Numerical variables were reported using the median (minimum-maximum) because the data distribution was not normal. The Shapiro–Wilk test was used for data distribution. Since the research groups consisted of 2 groups, the Mann–Whitney U test was used to compare the numerical values. The chi-square test was used for ratio comparisons according to research group. $P < .05$ was accepted as the statistical significance level.

3. Results

When we analyzed the data using the decision tree method, we observed that CRP is a very important parameter in the distinction between CAC and NCAC (Fig. 2). The first parameter to be checked in patients with a CRP level of >57 mg/L was age factor. WBC is an important parameter in patients over the age of 42 years; if WBC > 13,600/mm^3, the patient has CAC with a probability of 100%, and if the WBC count is 13,600 or less, the patient has NCAC with a probability of 100%. In patients ≤ 42 years of age, GBWT is an important parameter, if GBWT > 5.8 mm, the patient has CAC with a probability of 97%, and if GBWT ≤ 5.8 mm, the patient has NCAC with a probability of %100.

The first parameter to be evaluated in patients with a CRP level of ≤57 mg/L is the GBWT. In patients with a GBWT value above 4.85 mm, there is a 100% probability of CAC if age > 45 years, and NCAC with a probability of 83% if age ≤ 45 years. In patients with GBWT ≤ 4.85 mm, if NLR > 5.65 and WBC > 8100/mm^3, there is a 92% probability of CAC; if NLR > 5.65 and WBC ≤ 8100/mm^3, there is an 80% probability of NCAC. If NLR is ≤ 5.65 in patients with GBWT ≤ 4.85 mm, there is a 100% probability of NCAC (Fig. 2).

In the statistical analysis, a significant difference was found between the groups in terms of patient characteristics (Table 1) and laboratory ultrasonographic (Table 2) findings. When patient characteristics were analyzed statistically, male sex ($P < .001$), elderly patients ($P < .001$) and an ASA score of 3 ($P < .001$) were found to be significantly higher in the CAC

group. At the same time, the number of patients with Tokyo grade 3 ($P < .001$) patients and comorbid diseases were found to be significantly higher in the CAC group.

When the patients' laboratory ultrasonographic findings were analyzed, the albumin and CAR values, which were not included in the decision tree, were found to be significantly lower ($P < .001$), and significantly higher ($P < .001$), respectively, in the CAC group (Table 2).

4. Discussion

There are different aspects of CAC and NCAC treatment. Although the gold standard for NCAC is laparoscopic cholecystectomy (LC), in some risky situations, initial medical treatment followed by interval cholecystectomy can be performed to prevent mortality, morbidity, and consequently prolonged hospitalization. For CAC, although LC in the early period (within 72–96 hours) is the gold standard, open surgery or percutaneous cholecystostomy is recommended primarily because of the high risk of iatrogenic biliary tract or vascular injury due to fibrosis edema developing in the gallbladder in the late period.[9,10] Therefore, distinguishing between CAC and NCAC preoperatively in the early period is important for choosing the appropriate treatment method. Studies comprising scoring systems or predictive factors have been conducted to differentiate between CAC.[6,11,12] However, no studies in the literature have created an algorithm using the decision tree method. In this respect, our algorithm is the first in the literature.

In the decision tree algorithm we created, the CRP value was a very important parameter for the differentiation of CAC and NCAC. However, sex, Tokyo grade, ASA score, comorbid diseases (DM, COPD, CAD), and CAR did not have any effect on this differentiation. CRP is an acute-phase reactant produced by hepatocytes and may be elevated in many infectious, autoimmune, and cancerous diseases, including acute cholecystitis.[12] There are some studies in the literature that support our study and suggest that CRP may be an important predictive marker for CAC. Mahmood et al showed that a CRP value > 55 mg/L is an important marker for CAC.[2] Beliaev et al[13] stated that the risk of CAC is high in patients with CRP levels > 67 mg/L. In a study by Nikfarjam et al[14] CRP levels were significantly

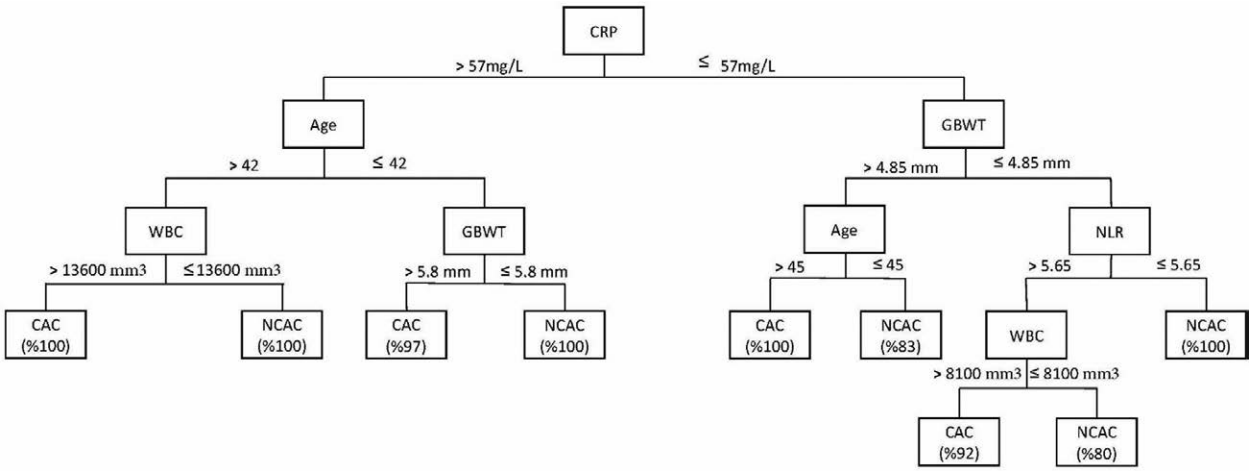

Figure 2. Algorithm developed with decision tree to detect complicated acute cholecystitis. CAC = complicated acute cholecystitis, CRP = C- reactive protein, GBWT = gallbladder wall thickness, NCAC = non-complicated acute cholecystitis, NLR = neutrophil lymphocyte ratio, WBC = White blood cell.

Table 1

Patients characteristics.

	Total (1034)	NCAC (n = 885)	CAC (n = 149)	*P* value*
Gender				
Female	649 (62.8%)	577 (65.2%)	72 (48.3%)	<.001
Male	385 (37.2%)	308 (34.8%)	77 (51.7%)	
Age	59 (13-93)	57 (13-93)	69 (31-93)	<.001†
ASA				
ASA 1	302 (29.2%)	274 (30.9%)	28 (18.8%)	<.001*
ASA 2	624 (60.3%)	541 (61.1%)	83 (55.7%)	
ASA 3	108 (10.4%)	70 (7.9%)	38 (25.5%)	
ASA 4	0	0	0	
ASA 5	0	0	0	
Tokyo grade				
Grade 1	810 (78.3%)	772 (87.2%)	0 (0%)	<.001*
Grade 2	204 (19.7%)	113 (12.8%)	124 (83.2%)	
Grade 3	20 (1.9%)	0 (0%)	25 (16.8%)	
CAD	115 (11.1%)	79 (8.9%)	36 (24.2%)	<.001*
COPD	39 (3.8%)	24 (2.7%)	15 (10.1%)	<.001*
DM	239 (23.1%)	169 (19.1%)	70 (47%)	<.001*

ASA = American Society of Anesthesiologists, CAC = complicated acute cholecystitis, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, NLR = neutrophil/lymphocyte ratio.

*Chi square test.

†Mann–Whitney *U* test (median (min–max)).

Table 2

Patient laboratory and ultrasonography findings.

	Total (n = 1034)	NCAC (n = 885)	CAC (n = 149)	*P* value
WBC	8.24 (2.29–36)	7.85 (2.47–29.7)	13.3 (2.29–36)	<.001*
NLR	2.20 (0.02–40.31)	2 (0.02–27.2)	7 (0.74–40.31)	<.001*
CRP	10 (0.22–363.6)	9.30 (0.22–297)	115.6 (2–363.6)	<.001*
Albumin	4 (2–38)	4 (2–38)	3.40 (2.29–4.70)	<.001*
CAR	2.50 (0.04–123)	2.40 (0.04–72)	38.4 (0.43–123)	<.001*
GBWT (mm)	3 (1–15)	3 (1–10)	5.50 (2–15)	<.001*

CAC = complicated acute cholecystitis, CAR = CRP/albumin ratio, CRP = C-reactive protein, GBWT = gallbladder wall thickness, NCAC = non-complicated acute cholecystitis, NLR = neutrophil/lymphocyte ratio, WBC = white blood cell.

*Mann–Whitney *U* test.

higher in gangrenous cholecystitis than in non-gangrenous cholecystitis (94 vs 17 mg/L). In our study, CRP was found to be significantly higher in the CAC group (9.3 vs 115.6 mg/L), which was consistent with the literature. Although CAR was not included in the decision tree, it was found to be statistically significantly higher in the CAC group. Although there is a study in the literature that high CAR predicts difficult laparoscopic cholecystectomy,[15] no study investigating its relationship with CAC has been found.

An increase in the number of WBCs and neutrophils in the blood indicates a severe inflammatory process.[16] In many previous studies, have shown that there is an increase in WBCs in the blood in severe inflammatory conditions of the gallbladder.[4] As expected in our study, the WBC value in the CAC group was found to be significantly higher than in the NCAC group and was an important parameter in the decision tree (CAC vs NCAC; 7.85 vs 13.3 mm^3; $P < .001$). Wu et al[6], Fagan et al and Önder et al[3,17], and Merriam et al[18] reported that WBC > 13.000/mm^3, WBC > 15.000 mm^3, and WBC > 17.000/mm^3, respectively, are important laboratory markers for the development of gangrenous cholecystitis. Previous studies have shown that, leukocytosis may result from an inflammatory response caused by gangrene or necrosis of the gallbladder and should always be taken seriously.

In cancer or severe inflammatory conditions, an increase in the NLR in the blood also occurs as a systemic inflammatory response in the patient's body. The increase in NLR was attributed to an increase in the secretion of proinflammatory cytokines in the plasma.[18,19] Some previous studies, have reported that a high NLR also has predictive value for CAC. Lee et al[20], Micic et al[21], Mahmood et al[2] showed that NLR > 3, NLR > 4.18, and NLR > 8, respectively, can be used in the differential diagnosis of CAC. Consistent with previous studies, in our study, the NLR was found to be significantly higher in the CAC group and was an important parameter in the decision tree (NLR critical value: 5.65).

Many studies have reported that the risk of developing CAC is increases with increasing age. Owing to venous insufficiency that worsens with advancing age, the vascular circulation of the gallbladder wall is impaired earlier in elderly patients; therefore, necrosis/perforation develops more frequently.[22,23] Therefore, another important parameter used in decision trees is the age factor. Some authors have considered being over the age of 40, some over the age of 45, and some over the age of 50 as risk factors for CAC.[24,25] In the decision tree we created, the critical age was 42 years in patients with CRP > 57 mg/L and 45 years in patients with CRP ≤ 57 mg/L.

World Society of Emergency Surgery (WSES) guidelines recommend ultrasonography as the primary imaging technique in the diagnosis of acute cholecystitis due to gallstones.[26] The rate of CAC diagnosis on preoperative ultrasonography varies around 9–10%.[27] On ultrasonography, findings such as pericholecystic fluid, pericholecystic abscess, wall irregularity, gallbladder distension, gallbladder wall defect, and increase in gallbladder wall thickness can be detected in patients with CAC.[28] Although none of these findings were specific enough, we included GBWT in our algorithm, considering the severe inflammation and edema of the gallbladder in CAC cases. In our study, a significant difference was found between NCAC and CAC in the terms of GBWT (3 vs 5.5 mm; $P < .001$). Many studies in the literature support our ultrasonography findings. In a study conducted by Sureka et al,[29] an increase in GBWT was found in 96.7% of the patients. In a series of 5812 cholecystectomy cases, Wu et al[6] showed that GBWT > 4.5 mm was significantly associated with gangrenous cholecystitis. In his study, Shapira-Rootman et al[27] stated that there was a significant increase in GBWT in the CAC group (5.6 vs 4.2 mm). However, contrary to this study, Yeh et al[5] found no significant difference between the groups in terms of GBWT.

The fact that this was a single-center study and the small sample size in the CAC group represent the limitations of this study.

6. Conclusion

CAC requires early diagnosis and urgent intervention before surgery. Early diagnosis is the most important method for reducing morbidity and mortality. Therefore, we believe that our algorithm will aid in the early diagnosis of CAC with high accuracy in centers with limited facilities. If our decision tree model is used, not only a significant reduction in patient mortality and morbidity, but also a cost-effective treatment can be achieved by avoiding unnecessary costs.

Author contributions

Conceptualization: Afig Gojayev, Emre Karakaya, Sedat Yıldırım.
Data curation: Afig Gojayev, Murathan Erkent, Lara Kavasoğlu, Cem Aydoğan.
Formal analysis: Murathan Erkent, Sait Can Yücebaş.
Investigation: Afig Gojayev, Murathan Erkent, Sait Can Yücebaş, Cem Aydoğan.
Methodology: Sait Can Yücebaş.
Project administration: Emre Karakaya, Sait Can Yücebaş.
Resources: Afig Gojayev.
Software: Hüseyin Onur Aydın.
Supervision: Emre Karakaya, Hüseyin Onur Aydın, Sedat Yıldırım.
Writing – original draft: Afig Gojayev.
Writing – review & editing: Emre Karakaya.

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