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C-Reactive Protein as Predictor of Acute Cholangitis in Patients with Acute Calculous Cholecystitis

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ABSTRACT

Objective: *Identify a marker of systemic inflammatory response that predicts acute cholangitis in patients with acute calculous cholecystitis.*

Materials and Methods: *Cross-sectional and retrospective study of patients with acute calculous cholecystitis who underwent endoscopic retrograde cholangiopancreatography for clinical diagnosis of acute cholangitis. Group A was obtained with 24 patients with acute calculous cholecystitis and acute suppurative cholangitis, and group B of 24 patients with acute calculous cholecystitis without acute suppurative cholangitis.*

Results: *A cut-off point of 34 years was obtained for a sensitivity, specificity and AUC for the diagnosis of acute suppurative cholangitis in patients with acute calculous cholecystitis of 95%, 41% and 74% (p=0.003), respectively, 83%, 79% and 86% (p=<0.001) for a C-reactive protein, respectively, with a cut-off point of 10.3 mg/dl, and 83%, 62% and 72% (p=0.007) for a neutrophil-lymphocyte ratio, respectively, for a cut-off point of 6.7.*

Conclusion: *C-reactive protein is the systemic inflammatory response marker with the greatest predictive capacity for acute cholangitis in acute calculous cholecystitis.*

Keywords

C-reactive protein, CRP, Acute cholangitis, Acute lithiasis cholecystitis.

Introduction

Benign biliary tract diseases represent one of the most common problems in developed countries and include gallbladder or bile duct disorders such as acute calculous cholecystitis (ACC), choledocholithiasis, acute cholangitis (AC), and/or acute biliary pancreatitis (ABP), all of which result from the presence of gallbladder stones (cholelithiasis). Cholelithiasis is observed in up to 15% of the Caucasian population, while the risk of developing any of these complications is 1% to 4% per year [1,2].

Acute cholangitis, also known as acute bacterial cholangitis or ascending cholangitis, is a condition caused by bacterial infection of the biliary system, commonly due to partial or complete obstruction of the common bile duct. Men and women are equally affected, with an average age of presentation between 50 and 60 years. A prevalence of Acute Biliary Cholangitis is known to be 6% to 9% in patients admitted to hospital for cholelithiasis [3].

Choledocholithiasis is the most common cause of biliary obstruction and represent the 85% of cases of Acute cholangitis. Other causes include benign or malignant bile duct strictures, pancreatic cancer, ampullary adenoma, among others. Two factors must be present to occur acute cholangitis: a) biliary infection, the

most common route being ascending from the duodenum, and b) increased intraductal pressure in the bile duct secondary to biliary ectasia [3,4].

Pressure of the common bile duct have an important role in the pathogenesis of acute cholangitis. When intraductal pressure exceeds 25 cm H_2O, cholangiovenous and cholangiolymphatic reflux may occur, expelling microorganisms or endotoxins into the systemic circulation, causing bacteremia and endotoxinemia with a heightened systemic inflammatory response [5].

For a long time, AC was diagnosed according to the Charcot triad (right hypochondriac pain, jaundice, and fever persisting for more than 24 hours), with highly specific, 95.9%, but low sensitivity, 26.4%, with a considerable false positive rate of 11.9% for acute calculous cholecystitis. Recently, multicenter studies have reported that the diagnostic rates of Charcot triad are even lower, at 26.4% and 21.2% [6,7].

In 2007, Tokyo Guidelines for the diagnosis and assessment of severity of acute cholangitis (TG07) added blood and imaging tests to the diagnostic criteria for AC for a sensitivity and specificity of 82.6% and 79.8%, respectively, with a 15.5% false-positive rate for ACL. Excluding abdominal pain, the TG07 diagnostic criteria provided a sensitivity of 91.8% and specificity of 77.7% for the diagnosis of AC and a false-positive rate for ACL of only 5.9%, and were designated as the diagnostic modality for acute cholangitis in the 2013 Tokyo Guidelines for the management of acute cholangitis (TG13). Currently, these latter criteria are adopted as the diagnostic criteria for AC in the new 2018 Tokyo Guidelines for diagnostic criteria and severity classification of acute cholangitis (TG18) (Table 1) [7,8].

Table 1.

A. Systemic inflammation	
A-1	Fever and/or chills: • Body temperature >38°C
A-2	Laboratory findings: • White blood cell count <4 or >10 (×1000/μL) • CRP ≥1 (mg/dL)
B. Cholestasis	
B-1	Jaundice: • Total bilirubin ≥2 mg/dL
B-2	Abnormal liver function tests: • Alkaline phosphatase >1.5 x URL • Gamma-glutamyl transferase >1.5 x URL • Aspartate aminotransferase >1.5 x URL • Alanine aminotransferase >1.5 x URL
C. Imaging	
C-1	Bile duct dilation
C-2	Evidence of etiology on imaging (stricture, stone, stent, etc.)
Suspected diagnosis: one item in A + one item in B or C **Definitive diagnosis:** one item in A, one item in B, and one item in C.	

Upper reference limit (URL), C-reactive protein (CRP).

The mortality rate for AC is high, exceeding 50% if biliary pressure is not relieved by biliary drainage. A diagnosis of acute suppurative cholangitis (ASC) is frequently made when purulent discharge from the ampulla of Vater is seen during ERCP. A significantly lower mortality rate, less than 10%, has been shown when biliary drainage is performed within 24 hours of diagnosis. This also leads to faster recovery, shorter hospital stays, and lower costs [9,10].

Systemic inflammatory response markers, such as C-reactive protein (CRP) and white blood cell count, can be very useful for diagnosing AC. CRP is an acute-phase protein synthesized and secreted by the liver in response to interleukin-6 (IL-6) and other proinflammatory cytokines. It has a half-life of 19 h and is responsible for activating the classical complement cascade and stimulating phagocytosis by immune cells [11].

The neutrophil-to-lymphocyte ratio (NLR) is an easy, reproducible, and inexpensive parameter for assessing a person's inflammatory status. It has been shown to be a predictor of inflammatory or infectious pathologies, including acute appendicitis, and even a predictor of survival in breast cancer. To calculate the NLR, it is necessary to divide the absolute neutrophil count by the absolute lymphocyte count. An elevated NLR reflects the activation of the inflammatory pathway due to the increased neutrophil count resulting from inflammatory components such as IL-6, tumor necrosis factor alpha (TNF-α), and granulocyte colony-stimulating factor [12,13].

ACC is an acute inflammatory process of the gallbladder wall due to a gallstone impacted in the infundibulum or cystic duct and is the most frequent complication of gallstone disease. ACC is diagnosed each year in approximately 200,000 people in the United States of America. With a prevalence of 5%, it is one of the most common causes of abdominal pain in patients attending the emergency department and accounts for one-third of hospital admissions for surgical emergencies [14].

On the other hand, the prevalence of choledocholithiasis in patients with ACC ranges between 7 and 20%. Endoscopic Retrograde Cholangiopancreatography (ERCP) is the gold standard for the diagnosis and treatment of choledocholithiasis, allowing for the complete removal of bile duct stones. Although choledocholithiasis warrants an endoscopic approach as soon as possible, there is no evidence of significant benefit in performing an ERCP early (less than 48 hours, if not accompanied by BPA), or urgently (within 24 hours, if not accompanied by AC) [15,16].

Both acute cholangitis and choledocholithiasis are entities that can present concomitantly in a patient with ACC, where the parameters of inflammation and cholestasis will be elevated in the same way, being the acute gallbladder process a distractor for the clinical diagnosis of AC. In the current literature, there are no studies of patients with AC concomitant with ALC where the behavior of inflammatory markers or their ideal cut-off points to discriminate between both pathologies can be observed, so the objective of this study was to evaluate the discriminatory power

of CRP for the diagnosis of AC in patients admitted with ALC and to determine its adequate diagnostic cut-off point with which an immediate aggressive therapy can be offered to patients with AC or to advocate for a management with a longer margin of time in the case of ALC without AC.

Materials and Methods

Retrospective, cross-sectional and analytical study of 24 patients with ACC and acute suppurative cholangitis, and 24 in the control group, patients with ACC without acute suppurative cholangitis on ERCP in adult patients undergoing ERCP for clinical diagnosis of AC by TG18 since november 2023 in retrospect. Those patient with evidence of any infectious focus concomitant with ACC that could alter the patient's inflammation tests were eliminated.

Results

In the univariate analysis, 54.2% (n=26) were women and the mean age was 51 years (SD± 18). 47.9% (n=23) reported fever and/or chills upon admission. The median leukocyte count was 10.0 X10*3/µL (Q1-Q3= 7.7-15.5), neutrophil count was 7.6 X10*3/µL (5.7-13.3), lymphocyte count was 1.0 X10*3/µL (0.7-1.6), Neutrophil-Lymphocyte Ratio (NLR) was 8.8 (3.1-17.2) and CRP was 10.8 mg/dl (3.3-23.1).

In the bivariate analysis, there were no significant differences between sex, gallbladder wall, longitudinal gallbladder diameter or liver function tests regarding the presence of acute suppurative cholangitis (p>0.05). There was a significant difference between the presence of fever and/or chills, age, white blood cell count, neutrophil count, lymphocyte count, NLR, and CRP regarding evidence of acute suppurative cholangitis (p<0.05) (Table 2).

In the construction of ROC curves, age had an AUC = 0.749 (p = 0.003, 95% CI [0.611-0.887]) with an optimal cut-off point of 34.5 years for a S of 95% and E of 42% through Youden index. The ROC curve for CRP showed an AUC = 0.862 (p = <0.001, 95% CI [0.758-0.966]) with an optimal cut-off point of 10.3 mg/dl, for a S of 83% and E of 80%. While the ROC curve of NLR identified an AUC = 0.727 (p = 0.007, 95% CI 0.578-0.875) with an optimal cut-off point of 6.7 for an S of 83% and E of 67%. The rest of the inflammation parameters presented an AUC less than 0.7, so their predictive capacity of AC is limited in the context of ACC.

Overall, a CRP ≥10.3 mg/dl and NLR ≥6.7 had the highest specificity, 91%, compared to the combination of age ≥34 years and CRP ≥10.3 mg/dl, which was 83%. In terms of clinical practice, the highest probability of presenting acute suppurative cholangitis is provided by the combination of CRP ≥10.3 mg/dl and NLR ≥6.7, with a PPV of 90%, while the highest probability of

Table 2.

Variables		Total (n=48)	Cholangitis		p
			No (n=24)	Yes (n=24)	
Sex	Women	26 (54.2%)	12 (50%)	14 (58.3%)	0.562
	Men	22 (45.8%)	12 (50%)	10 (41.7%)	
Fever and/or chills	No	23 (47.9%)	17 (70.8%)	6 (25%)	**0.001**
	Yes	25 (52.1%)	7 (29.2%)	18 (75%)	
Age (years old) *		51 (18)	43 (17)	58 (15)	**0.003**
Leukocytes (x10*3/µL) **		10.0 (7.7-15.5)	8.3 (6.6-13.3)	11.5 (8.8-16.9)	**0.041**
Neutrophils (x10*3/µL) **		7.6 (5.7-13.3)	6.45 (4.2-10.6)	10.0 (6.5-15.3)	**0.020**
Lymphocytes (x10*3/µL) **		1.0 (0.7-1.6)	1.59 (0.7-2.3)	0.8 (0.7-1.2)	**0.022**
NLR **		8.8 (3.1-17.2)	3.53 (2.5-11.3)	10.2 (8.0-17.9)	**0.007**
CRP (mg/dl) **		10.8 (3.3-23.1)	4.0 (1.0-8.74)	21.6 (14.1-26.9)	**<0.001**
TB (mg/dl) **		6.7 (3.4-11.5)	5.8 (2.9-8.8)	9.0 (4.0-16.1)	0.063
DB (mg/dl) **		4.2 (1.9-6.9)	3.8 (1.5-5.7)	5.7 (2.1-9.0)	0.066
IB (mg/dl) **		2.3 (1.4-3.6)	2.1 (1.4-3.0)	2.7 (1.8-5.0)	0.132
ALT (UI/l) **		179 (99-340)	271 (108-513)	131 (97-221)	0.055
AST (UI/l) **		144 (81-230)	190 (78-230)	137 (81-188)	0.392
GGT (UI/l) **		575 (299-895)	640 (284-1042)	521 (310-763)	0.632
AP (UI/l) **		306 (198-503)	283 (196-379)	359 (227-573)	0.287
LDH (UI/l) **		247 (189-290)	262 (191-310)	231 (186-285)	0.407
Common bile duct diameter (mm) **		8.3 (7.9-11.5)	8.0 (6.5-9.5)	9.0 (8.0-12.0)	**0.018**
GB wall (mm) **		4.0 (4.0-5.0)	4.0 (4.0-5.0)	4.0 (4.0-5.0)	0.596
GB longitudinal diameter (cm) *		7.8 (2.5)	7.3 (2.5)	8.2 (2.4)	0.236
GB Transverse diameter (cm) *		3.8 (1.0)	3.3 (0.8)	4.2 (1.1)	**0.004**

Neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), total bilirubin (TB), direct bilirubin (DB), indirect bilirubin (IB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), gallbladder (GB).

not presenting it originates in patients under 34 years of age, with a NPV of 90% (Table 3).

In the multivariate binary logistic regression of variables with significant differences between groups (age, fever and/or chills, leukocytes, neutrophils, lymphocytes, NLR, CRP, common bile duct diameter, transverse diameter of BV) a predictive effect was found for age, with an OR of 1.222 (p=0.026, 95% CI [1.014-1.242]) and CRP, with an OR of 1.246 (p=0.022, 95% CI [1.033-1.504]) for the presence of acute suppurative cholangitis in ERCP in patients with ACC, with a predicted percentage of 91.7% (Table 4).

Table 3.

Variable	S	E	PPV	NPV
Age ≥ 34 años	95%	41%	62%	90%
CRP ≥10.3 mg/dl	83%	79%	80%	82%
NLR ≥6.7	83%	62%	68%	78%
Age ≥ 34 años + CRP ≥10.3 mg/dl	79%	83%	82%	80%
CRP ≥10.3 mg/dl + NLR ≥6.7	75%	91%	90%	78%

Neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), sensitivity (S), specificity (E), positive predictive value (PPV), negative predictive value (NPV).

Table 4.

Variables in the equation	p	OR	IC 95%	
			Lower	Upper
Age	**0.026**	**1.122**	**1.014**	**1.242**
Fever and/or chills (yes)	0.157	0.112	0.005	2.313
Leukocytes	0.824	1.424	0.063	32.206
Neutrophils	0.744	0.581	0.022	15.184
Lymphocytes	0.343	0.196	0.007	5.705
NLR	0.464	0.965	0.876	1.062
CRP	**0.022**	**1.246**	**1.033**	**1.504**
Common bile duct diameter	0.079	1.797	0.934	3.457
GB Transverse diameter	0.095	3.691	0.795	17.130

Variables included in the equation: Age, fever, leukocytes, neutrophils, lymphocytes, neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), common bile duct diameter, and gallbladder (GB) transverse diameter. Predicted percentage: 91.7%.

Discussion

Currently, the TG13/TG18 diagnostic criteria achieve a sensitivity of 91% and a specificity of 77% for the diagnosis of AC, however, due to their low cut-off points in inflammatory parameters there is a considerable number of false positives due to ACC. Beliaev AM et al., in 2015 showed a PCR cut-off point of 3.05 mg/dl for a sensitivity and specificity of 84% and 89%, respectively, for the diagnosis of any grade of ACC, which show how ease is ACC yield a false positive for CA [17].

Beliaev AM et al., at 2018, demonstrated a CRP cut-off point greater than 2.35 mg/dL for a sensitivity, specificity, and AUC of 77%, 100%, and 88%, respectively, for the diagnosis of AC, and 68%, 95%, and 82% for an NLR greater than 5.3, respectively. This study demonstrated that CRP is the marker with the greatest discriminatory power for the diagnosis of AC; however, this study does not consider concomitant acute inflammation of the gallbladder. In our study, we demonstrated higher CRP and NLR cut-offs for the diagnosis of AC in concomitant with ACC, with sensitivity, specificity and AUC of 83%, 79% and 86%, respectively, for CRP greater than 10.3 mg/dl, and 83%, 62% and 72% for NLR of 6.7, respectively. Similarly, in clinical practice, the highest probability of presenting AC in patients with ACC is found when both cut-offs are positive, CRP greater than 10.3 mg/dl and NLR greater than 6.7 [18].

In the other hand, Díaz-Flores A, et al., 2017, in their study with a Mexican population, demonstrated a CRP greater than 11 mg/dl as a predictor of difficult cholecystectomy, while Menéndez-Sánchez P, et al., 2019, observed a CRP greater than 10.7 mg/dl as a predictor of gangrenous ALC. Therefore, we can infer that in the case of acute gallbladder disease with marked local inflammation (gangrenous or emphysematous, pericholecystic abscess, etc.), the cut-off points obtained in this study may lose diagnostic accuracy [14,19].

Conclusion

CRP and NLR are the most useful inflammatory response markers for predicting AC in patients with concomitant CLA, for a cut-off point of ≥10.3 mg/dl and ≥6.7, respectively, both with a sensitivity of 83%. Furthermore, the combination of CRP ≥10.3 mg/dl and NRL ≥6.7 shows the highest probability of demonstrating AC in patients with ACC with a PPV of 90%, patients who benefit from an urgent ERCP. However, the highest probability of not presenting AC is when the age is younger than 34 years, with a NPV of 90%. Based on all the above, we concluded that CRP is the systemic inflammatory marker with the greatest predictive capacity for suppurative AC in patients with ACC.

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