Clinical Implications of Hepatobiliary Scintigraphy and Ultrasound in the Diagnosis of Acute Cholecystitis

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Original research

Clinical implications of hepatobiliary scintigraphy and ultrasound in the diagnosis of acute cholecystitis

Limael E. Rodriguez*, Luis E. Santaliz-Ruiz, Gabriel De La Torre-Bisot, Giovanni Gonzalez, Miguel A. Serpa, Felipe Sanchez-Gaetan, Jorge L. Martinez-Trabal, Julio A. Peguero-Rivera, Guillermo Bolanos-Avila

Department of Surgery, St. Luke's Memorial Hospital, Ponce Health Sciences University, Ponce, PR, USA

HIGHLIGHTS

- For acute cholecystitis, US had a sensitivity and specificity of 26% and 80%. HIDA scan had a sensitivity and specificity of 87% and 79%.
- Glucose >140 mg/dL, age >50, and WBC count >10 ($\times 10^9$ /L) were independent clinical features associated with histologically confirmed acute cholecystitis.
- Delayed HIDA scan protocol resulted in increased time to surgery, length of stay, and increased costs.

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ABSTRACT

Background: We assess the performance of ultrasound (US) and hepatobiliary scintigraphy (HIDA) as confirmatory studies in acute cholecystitis (AC) and demonstrate our current imaging protocol's impact on outcomes.

Study design: Between January 2013 to July 2014, 117 patients were admitted through the emergency room with a preliminary diagnosis of AC. Overall, 106/117 (91%) of the patients received US preadmission and 34/117 (29%) received a HIDA post admission. Primary end points included: 1) diagnostic test reliability for AC, and 2) outcome and quality measures (time to surgery, LOS, costs, etc.).

Results: Laparoscopic cholecystectomy was performed in 96/117 (82%) and open cholecystectomy in 21/117 (18%) of the patients. Overall, histopathologic features consistent with AC was present in 46/117 (39%). AC alone was present in 23/117 (20%), and AC superimposed on chronic cholecystitis was present in 23/117 (20%). For AC, US had a sensitivity and specificity of 26% and 80%, respectively. HIDA scan had a sensitivity and specificity of 87% and 79%, respectively. Time to surgery (TTS) was 4 vs 2.3 days in patients who received HIDA vs US alone ($p = 0.001$), and length of stay (LOS) was 6.7 vs 4.3 days, respectively ($p = 0.001$). Age >50 years, glucose >140 (mg/dl), and WBC count >10 ($\times 10^9$ /L) were statistically significant independent variables associated with AC.

Conclusion: HIDA scan is superior to US as a diagnostic study in the setting of AC. Our current protocol of delayed HIDA (post-admission) was associated with increased TTS, LOS, and overall costs. Early confirmation with HIDA in high risk patients may hasten treatment allocation and improve outcomes in the setting of AC.

1. Introduction

Acute cholecystitis (AC) is a common surgical disease that requires prompt and precise diagnosis to improve outcomes. According to Tokyo guidelines, no single physical exam finding or laboratory test carries sufficient weight to establish or exclude AC, and an imaging study should be used to confirm the diagnosis [1,2]. In this study, we evaluated the performance of ultrasound (US) vs hepatobiliary scintigraphy (HIDA) as confirmatory imaging tests for AC and assessed our current imaging protocol's effect on outcomes.

2. Methods

From January 2013–July 2014, 117 consecutive patients

* Corresponding author.
E-mail address: lerodriguez26@yahoo.com (L.E. Rodriguez).

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presented to the emergency room (ER) with suspected acute cholecystitis. All patients received ultrasound and/or HIDA scan before surgical intervention. For the latter test, our institutional protocol required patients to be admitted to the surgery service (two surgeon experience) to proceed with HIDA scan, and the decision to use HIDA scan was at the discretion of the surgeon. All patients would eventually undergo laparoscopic or open cholecystectomy and a final histopathologic diagnosis with our institutional pathologist. Inclusion criteria was as follows: 1) admission through ER for suspected AC, and 2) received imaging study with US and/or HIDA scan. Exclusion criteria was as follows: 1) serum pancreatic lipase above 200 U/L and/or admission diagnosis of acute pancreatitis (n = 8), and 2) patients that did not receive imaging studies (n = 11). The cross sectional study was approved by our academic affiliate Ponce Health Sciences University IRB.

3. Imaging protocol

3.1. Ultrasound

Most patients underwent abdominal US in the emergency room setting. Sonographic analysis was carried out by our institutional radiologist at presentation, and we did not change the original radiologic interpretation. The final US interpretation was determined as follows:

- Findings consistent with AC: sonographic Murphy sign, pericholecystic fluid, gallbladder distension (>4 cm short axis), and/or thickening of the gallbladder wall (>4 mm). Visualization of one of the 4 major signs was interpreted as positive for AC.
- Cholelithiasis: Visualization of none of the above four signs with gallstones.

3.2. HIDA

A dynamic biliary study was performed following the intravenous administration of 6.1 mCi of Tc-99m Choletec (a hepatobiliary radiopharmaceutical agent). Sequential scintigraphic images of the abdomen in the anterior projection up to 60 min was done to evaluate for radiotracer distribution/activity throughout the hepatic parenchyma, intrahepatic ducts, gallbladder, common bile duct, and small bowel at 60 min. If no visualization of the gallbladder was present 1 hour into the study, morphine (5 mg) was given intravenously in order to stimulate retrograde filling of the gallbladder. If there was no visualization of the gallbladder at 30 min following morphine administration in the proper clinical setting, this scintigraphic finding was determined to be acute cholecystitis.

4. Pathological diagnosis

The histopathological criteria used in the analysis of gallbladder specimens were as follows:

- Absence of cholecystitis: normal gallbladder and/or absence of lymphocytic infiltration.
- Acute cholecystitis (AC): transmural neutrophilic infiltration ± involvement of adventitia (pericholecystitis) ± gangrene.
- Chronic cholecystitis (CC): lymphocytic infiltrates without neutrophilic infiltrates.
- Acute superimposed on chronic cholecystitis (ACC): the presence of acute and chronic features as noted above.
- Acalculous Cholecystitis: AC or ACC without gallstones.

A cost analysis was carried out by identifying mean payments made by “la Reforma” (the universal insurance in Puerto Rico) to our institution as follows: 1) each impatient day for diagnosis of AC and coverage of medications ($630.00), 2) US costs ($36.67), 3) HIDA scan ($97.95).

Statistical analysis was performed using the IBM SPSS version 21 (IBM Co., Armonk, NY, USA). Continuous data are reported as mean ± standard deviation. Nominal data are reported as percentages and/or number of subjects. A patient was classified as true-positive (TP) if the diagnosis of AC was retained on the final pathology report and the sign or the association of signs on the imaging test (HIDA or US) was indicative of AC. A patient was classified as true-negative (TN) if the diagnosis of AC was not retained and the sign or the association of signs was not indicative of AC. A patient was classified as false-positive (FP) if the diagnosis of AC was not retained but the sign or the association of signs was indicative of AC. A patient was classified as false-negative (FN) if the diagnosis of AC was retained but the sign or the association of the signs was not indicative of AC. The sensitivity was defined as TP/(TP+FN) and the specificity was defined as TN/(FP+TN). The positive likelihood ratio (LR+) was defined as sensitivity/1-specificity and the negative likelihood ratio was defined as 1-sensitivity/specificity.

5. Results

5.1. Population

A total of 117 patients (40 men and 77 women) were admitted through ER with suspected AC. Of these 106/199 (91%) received US in ER, and 34/117 (29%) received HIDA scan. Of the latter, 23/34 received HIDA scan alone. Mean age was 44 ± 18 years, and woman were the most common sex (baseline characteristics are summarized in Table 1).

5.2. Operative outcomes

Laparoscopic cholecystectomy was performed in 96/117 (82%) and open cholecystectomy in 21/117 (18%) of the patients. Of the latter, 15/21 (71.4%) were conversions to open technique due to inability to visualize anatomy because of inflammation (n = 7) and gangrene (n = 8). Six patients were treated with a planned open technique. There was no intraoperative mortality.

5.3. Histopathology outcomes

Overall, histopathologic features consistent with AC were present in 46/117(39%) (Fig. 1). AC alone was present in 23/117 (20%), and ACC was present in 23/117(20%). Gallstones were found in 91/117(78%) of the specimens. Overall, CC was the most common final diagnosis with a frequency of 71/117 (61%). Acalculous cholecystitis was found in 7/117 (6.7%). Acute cholecystitis with gangrene was present in 15/117 (12%) of the patients.

Table 1
Baseline characteristics for 117 admitted with acute cholecystitis.

Characteristic	Mean (SD)
Age (yrs)	44 (18)
Female/male ratio	77/40
BMI (kg/m^2)	30 (6)
WBC ($\times 10^9$/L)	13 (5.3)
Lipase (U/L)	149 (79)
AST (U/L)	39 (73)
ALP (U/L)	118 (73)
Total Bilirubin (mg/dl)	0.87 (1.3)

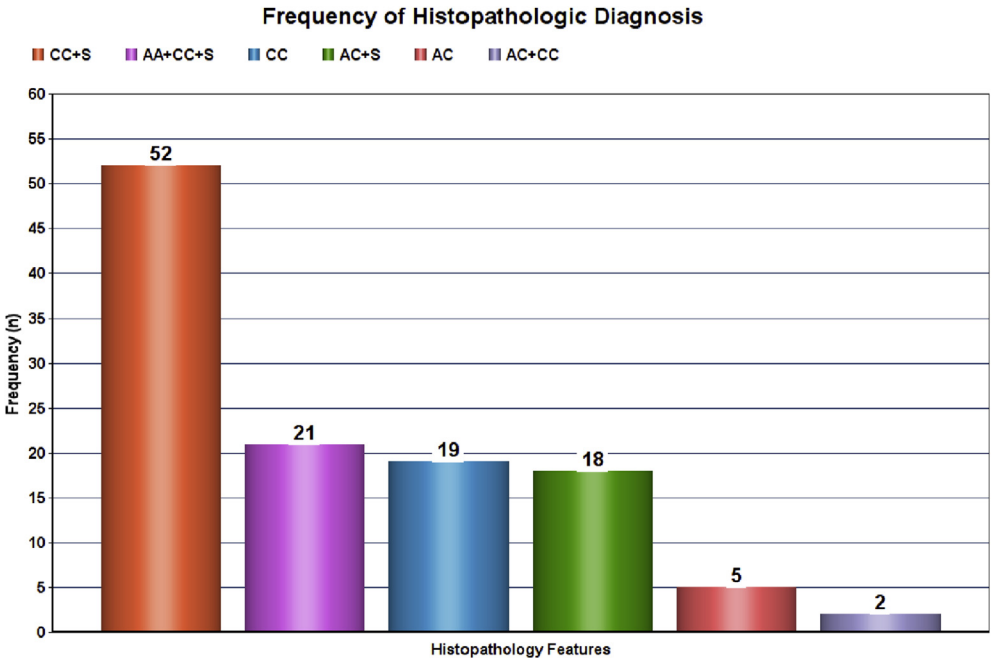

Fig. 1. Frequency of histopathologic diagnosis. AC = Acute Cholecystitis. CC=Chronic Cholecystitis. S=Gallstones.

5.4. Ultrasonography performance for AC

Twenty four (22.6%) patients had sonographic evidence of AC. Sensitivity, specificity, positive and negative likelihood ratios of ultrasonography were 26%, 80%, 1.29, and 0.93, respectively (Table 2). There were 31 false negative results, and 13 false positive results.

5.5. HIDA performance for AC

Seventeen patients had a positive HIDA scan for AC. Sensitivity, specificity, positive and negative likelihood ratios of HIDA were 86.7%, 79%, 4.13, and 0.17, respectively (Table 3). There were 2 FNs results, and 4 false positive results.

5.6. Clinical/quality outcomes

There was no post-operative mortality. Two patients treated with laparoscopic technique developed bilioma and both were treated with ERCP/stenting, respectively. Two patients that required open technique developed a right pleural effusion and hypoxemia that were managed conservatively. One patient treated with open technique developed a surgical site infection that was treated with drainage and IV antibiotics. Admission to surgery time and total length of stay were longer in patients who received HIDA scan vs US alone (Table 4). There was no difference in surgery to discharge time. Patients that received HIDA scan had higher overall cost to the payer ($2,727 vs $4,328, p = 0.001).

5.7. Multivariate analysis

Multivariate analysis demonstrated that glucose >140 mg/dL, age >50, and WBC count $>10 \times 10^9$ /L were statistically significant independent clinical features that were associated with histologically confirmed AC (Table 5). The regression coefficient for the latter factors was 1.5, 1, and 1, respectively. Using these coefficients as a score, ≥ 2 points was associated with a higher likelihood of AC ($p < 0.001$) (Table 6). Sex, BMI, elevated AST, ALP, and lipase were not found to be independent features associated with acute cholecystitis.

6. Discussion

Although historically a clinical diagnosis, acute cholecystitis in the modern era incorporates the use of clinical labs and imaging to make the diagnosis. The Tokyo guidelines have been widely adopted, with key recommendations as follows: 1) physical exam consistent with acute abdomen, 2) leukocytosis and an elevated inflammatory marker (i.e. CRP), and 3) confirmatory imaging (i.e. US, HIDA, CT, or MRI). For the latter, the recommendation leaves the confirmatory imaging test to the clinician's preference. For the past 40 years, ultrasound has been the imaging test of choice in the setting of AC. In a recent metanalysis, Kiewet et al. pooled all available studies related to imaging in AC, and were able to make pertinent observations related to the utility of these available imaging modalities (see Table 7) [3]. They showed that the utility of US may be overvalued due to frequent equivocal findings, substantial margin for error, and lower sensitivity and specificity related to

Table 2
Ultrasound diagnostic performance in acute cholecystitis. Sensitivity = 26.2%. Specificity = 79.7% Positive likelihood ratio (+) = 1.29. Negative likelihood ratio (−) = 0.93.

Ultrasound result	Pathology AC (+)	Pathology AC (−)
AC (+)	11	13
AC (−)	31	51
Total	42	64

Table 3
HIDA diagnostic performance in acute cholecystitis. Sensitivity = 86.7%. Specificity = 79.0%. Positive likelihood ratio (+) = 4.13. Negative likelihood ratio (−) = 0.17.

HIDA result	Pathology AC (+)	Pathology AC (−)
AC (+)	13	4
AC (−)	2	15
Total	15	19

Table 4
Comparison of patients who received ultrasound alone versus HIDA scan.

Outcome	US alone (n = 106)	HIDA (n = 34)	Difference	p-value
Length of Stay (mean days)	4.3	6.7	2.4	0.001
Admission to Surgery (mean days)	2.3	4	1.7	0.001
Surgery to Discharge (mean days)	3	3.6	0.6	0.34
Age (mean years)	42.8	49.6	6.8	0.09
Mean amount paid (US dollar) to our institution*	$2,727	$4,328	$1,601	0.001

*Note, cost analysis includes amount paid to institution per day (one set payment for the diagnosis of acute cholecystitis = $630/day) and imaging studies (HIDA = $97.95 and US = $36.67, respectively). Amount paid to the surgeon and operative/anesthesia costs were not included in the analysis.

Table 5
Regression analysis of independent variables associated with acute cholecystitis.

Variable	Odds ratio	95%	C.I.	Coefficient	p-value
Age ≥50 years	2.75	1.12	6.71	1.01	0.03
Glucose≥ 140	4.81	1.31	17.6	1.57	0.02
WBC ≥10	2.92	1.18	7.22	1.07	0.02
Male sex	1.38	0.5	3.47	0.32	0.49

Table 6
Cross table of independent clinical findings at presentation associated with histologically confirmed acute cholecystitis. Glucose >140 mg/dl = 1.5 points, Age >50 years = 1 point, and WBC >10 × 10^9 per liter (L = 1 point, respectively. As the score increases, the likelihood of AC increases accordingly (X^2 for trend = 24.4, $p < 0.001$). Note, points derived from the regression coefficient.

	Final pathology: Acute cholecystitis		
Score	No	Yes	Total
0	33	5	38
	87%	13%	
1	25	16	41
	61%	39%	
1.5	2	1	3
	67%	33%	
2	9	11	20
	45%	55%	
2.5	1	3	4
	25%	75%	
3.5	1	10	11
	9	91%	
Total	71	46	117

heterogeneous operator interpretations and diagnostic criteria. In this same study, the HIDA scan remained the gold standard with a mean sensitivity of 96% and a specificity 90% for AC. Our study was consistent with available literature and confirmed that HIDA was superior to US as a confirmatory test for AC [3]. CT and MRI are of potential value but lack studies that confirm their utility in the setting of AC [4–7].

Poorer outcomes when surgery is delayed for more than 72 hrs has been well described [8]. Most studies have demonstrated an increased LOS in hospital, which is usually related to one or more of the following: 1) non-resolution of symptoms or recurrence before planned operation, 2) gallstone (pancreatitis, cholangitis, etc.) related morbidity during waiting period, and 3) conversions to open related to inability to visualize anatomy via laparoscope at the time of intervention [8]. To our knowledge no studies have demonstrated that delayed imaging confirmation as the primary reason for delay to surgery. In our center, HIDA is utilized at the discretion of the surgeon and the current institutional policy requires admission before a HIDA scan can be performed. This delay in confirmation has effectively placed the patient at risk for poorer outcomes due to a delay in treatment. Moreover, our data showed increased costs to the payer with our delayed HIDA protocol. The admission to surgery time was double when HIDA was used, which resulted in increased LOS. The admission to surgery time was doubled when HIDA was used, which resulted in increased LOS.The latter was the most significant variable that increased cost to the payer, as our institution receives a bundled payment per day for the diagnosis of AC. However, there is a predetermined payment amount which has a limited number of days for the diagnosis of AC. Therefore, extended length of stay could result in significant losses to the institution.

Leukocytosis, age, and hyperglycemia were independent clinical features that increased the probability that the patient had AC. These findings are consistent with literature reports that have assessed prognostic factors for AC [9–11]. Using the regression coefficient, we were able to create a clinical score that can be utilized to help differentiate a high risk patient in the setting of AC. We propose that the presence of two of these features when AC is suspected is means to classify this patient as high risk, and an imaging modality other than US should be used to confirm the diagnosis. In our institution the HIDA scan is readily available and in the future we will carry out a prospective trial where immediate HIDA scan will be performed in the ER setting. We propose an algorithm to provide the emergency room physician criteria for utilization of HIDA when AC is suspected (Fig. 2). Depending on the result, and reevaluation post study, we will manage the patients accordingly.

Table 7
Comparison of available imaging modalities in the setting of acute cholecystitis.

Imaging Modality	Sensitivity (Sn) Specificity (Sp) *Mean % (range)*	Pros	Cons
Ultrasound	Sn 81% (50–100) Sp 83% (33–100)	Sensitive for gallstones, inexpensive, global assessment	Detection of small stones, sludge, or subtle pericholecystic changes. confusion with global anatomical features, operator dependence
HIDA	Sn 96% (78–100) Sp 90 (50–100)	Gold standard, high sn/sp, dynamic study	Not readily available, time consuming, requires nuclear team, confined to HB tract
CT SCAN	Sn 94% (89–100) Sp 59% (89–100)	Global assessment, readily available, high sn/sp	Very limited data, radiation exposure
MRI	Sn 85% (50–91) Sp 81% (78–89)	Global assessment, diagnostic accuracy similar to US	Limited data, time consuming, few advantages over CT scan, lack of availability

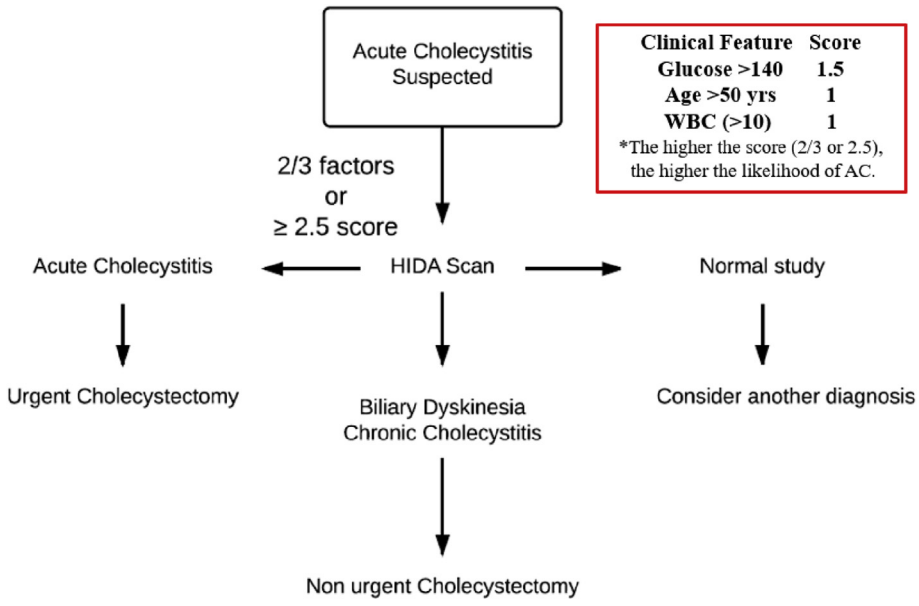

Fig. 2. Algorithm and management for imaging when acute cholecystitis is suspected.

A main limitation of this study is the retrospective observational design. The use of HIDA and treatment were determined by individual preferences of the surgeon. A prospective randomized study is needed to better understand the utility and timing of confirmatory test in the setting of acute cholecystitis. Another limitation is the relatively small number of patients and the study may have benefited from extending our data collection to more years (i.e. >1.5 years).

In closing, imaging studies play an important role in the diagnosis of acute cholecystitis. As expected, HIDA scan was superior to US as a confirmatory test for AC. We believe that an early confirmation protocol in high risk patients will effectively hasten our time to diagnosis, which should result in a significant improvement in time to surgery and outcomes.

Ethical approval

The study was approved by our academic affiliate Ponce Health Science University IRB.

Sources of funding

None.

Author contribution

Study conception and design: Limael Rodriguez MD, Jorge Martinez-Trabal MD FACS, Miguel Serpa MD, Felipe Sanchez Gaetan MD, Julio Peguero MD, Guillermo Bolanos MD FACS.

Acquisition of data: Limael Rodriguez MD, Luis Santaliz MD, Gabriel De La Torre MD, Giovanni Gonzalez MD.

Analysis and interpretation of data: Limael Rodriguez MD, Jorge Martinez-Trabal MD FACS , Felipe Sanchez Gaetan MD, Julio Peguero MD, Guillermo Bolanos MD FACS. The authors would like to thank Dr. Ivan Iriarte for the statstical analysis of our data.

Drafting of manuscript: Limael Rodriguez MD, Luis Santaliz MD.

Critical revision: Limael Rodriguez MD, Jorge Martinez-Trabal MD FACS, Miguel Serpa MD, Julio Peguero MD, Guillermo Bolanos MD FACS.

Conflicts of interest

None.

Guarantor

Guillermo Bolanos-Primary Investigator.

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