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Abdominal ultrasound *versus* hepato-imino diacetic acid scan in diagnosing acute cholecystitis—what is the real benefit?

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ABSTRACT

Background: Acute cholecystitis is one of the most common surgical problems, yet substantial debate remains over the utility of simple examination, abdominal ultrasound (AUS), or advanced imaging such as hepato-imino diacetic acid (HIDA) scan to support the diagnosis.

Materials and methods: The preoperative diagnostic workup of patients who underwent cholecystectomy with histologically confirmed acute cholecystitis was reviewed to calculate the sensitivity of AUS, HIDA scan, or both. In addition, the sensitivity of the commonly described ultrasonographic findings was assessed.

Results: From 2010 through 2012, 406 patients among 9087 reviewed charts presented to the emergency department with acute upper abdominal pain and met inclusion criteria. 32.5% ($N = 132$) of patients underwent AUS only, 11.3% ($N = 46$) underwent HIDA scan only, and 56.2% ($N = 228$) had both studies performed for workup. 52.7% ($N = 214$) of patients had histopathologically confirmed acute cholecystitis. The sensitivities of AUS, HIDA, and AUS combined with HIDA for acute cholecystitis were 73.3% (95% confidence interval [CI] = 66.3%–79.5%), 91.7% (95% CI = 86.2%–95.5%), and 97.7% (95% CI = 93.4%–99.5%), respectively. Although of limited sensitivity, AUS findings of sonographic Murphy sign, gallbladder distension, and gallbladder wall thickening were associated with a diagnosis of acute cholecystitis.

Conclusions: The sensitivity of AUS for diagnosing acute cholecystitis in patients with acute upper abdominal pain is limited. The addition of a HIDA scan in the diagnostic workup significantly improves sensitivity and can add valuable information in the appropriate clinical setting.

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1. Introduction

Ten to twenty percent of Americans have gallstones, and each year up to 3% of them experience symptoms of biliary colic [1,2]. Acute cholecystitis will develop in about 20% of this patient population [3]. The overwhelming majority of those will present to the Emergency Department with complaints of upper abdominal pain. Accurate diagnosis in a timely fashion is essential to initiate treatment and prevent unnecessary morbidity and mortality. Despite a thorough history and physical examination by experienced physicians, the diagnosis is frequently ambiguous requiring more comprehensive and at times laborious diagnostic imaging evaluation. A recent clinical review in the Journal of the American Medical Association concluded that no single clinical finding or laboratory test carries sufficient weight to establish or exclude acute cholecystitis without further testing [4].

Several investigators have previously examined the role of abdominal ultrasound (AUS) in the diagnosis of acute cholecystitis [5–7]. Multiple sonographic indicators for acute cholecystitis have been described including the presence of gallstones, gallbladder wall thickening, gallbladder distension, pericholecystic fluid, and a sonographic Murphy sign [8–10]. However, the impact of different combinations of ultrasonographic findings on the diagnosis of acute cholecystitis has not been established. Hepato-imino diacetic acid (HIDA) scan is a well-established scintigraphic technique that is used as an alternative or complementary modality for the diagnosis of acute cholecystitis. Although it has been shown to have higher sensitivity, specificity, and diagnostic accuracy when compared with ultrasonography, the individual studies contain a small number of subjects [7,11]. Furthermore, despite the superior sensitivity of HIDA scan for the diagnosis of acute cholecystitis, physicians seem to be reluctant to use HIDA scan, and ultrasonography continues to be the most commonly used imaging modality for suspected cholecystitis.

The aim of this study was to determine the sensitivity of AUS, HIDA scan, and the combination of both studies for acute cholecystitis in a selected patient population who presented to the Emergency Department with acute upper abdominal pain and suspected diagnosis of acute cholecystitis, and who later underwent cholecystectomy. We also investigated the relationship of various commonly described ultrasonographic findings to histologically proven acute cholecystitis.

2. Methods

Prospectively collected data of patients presenting to the Emergency Department with acute upper abdominal pain from January 2010 through October 2012 was retrospectively reviewed. If patients had undergone AUS and/or HIDA scan and cholecystectomy within 5 d of the initial presentation, they were included in the analysis. This study was performed by the Department of Surgery at St. Joseph Mercy Hospital, Ann Arbor, MI, and approved by the Institutional Review Board. Clinicopathologic data included patient demographics, AUS findings, HIDA scan results, intraoperative findings, and histopathologic results. Patients were excluded if they had no available imaging, did not undergo cholecystectomy, or had gallstone pancreatitis. In addition, pregnant women, prisoners, and patients under 18 y were excluded, as well as cases in which there were technical difficulties in obtaining adequate views of the gallbladder on AUS, longer than 5 d interval between initial presentation and surgery, and the presence of pathology such as ascites, severe right sided heart failure, hypoproteinemia, or multiple myeloma that would make ultrasound assessment difficult and/or inaccurate.

2.1. *Diagnosis of acute cholecystitis*

Patients were considered to have acute cholecystitis on AUS, if a diagnosis of "acute cholecystitis" or "likely or equivocal acute cholecystitis" was given by a board-certified, attending radiologist based on the constellation of the AUS findings. Several AUS finding were taken into account including the presence of sonographic Murphy sign, gallbladder wall thickening >5 mm, presence of pericholecystic fluid, and presence of hydrops with increased transverse gallbladder diameter. Presence and location of stone(s) or sludge were also taken into consideration. Radiology reports where any of these findings were listed as not present or were not noted were considered to be negative for the finding.

An HIDA scan was considered positive if the imaging study, as assessed by an attending radiologist, was read as acute cholecystitis or if the gallbladder was not visualized (i.e., persistent cystic duct obstruction through the imaging sequence was noted) and partial or complete common bile duct obstruction was not suggested. In our institution, Technetium-99m mebrofenin is used as our tracer in a dose of 5 mCi. The patient is fasted for at least 2 h before the test. If the patients have been fasting for more than 24 h, they are pretreated with a short (3 min) cholecystokinin infusion 30 min before injecting the tracer. If the gallbladder was not visualized at 60 min despite common bile duct and/or gut visualization, morphine was injected intravenously at a dose of 0.04 mg/kg of body weight to close the sphincter of Oddi and raise common bile duct pressure. If the gallbladder was visualized within 30 min of the morphine injection, a diagnosis of chronic cholecystitis was made. If the gallbladder was not visualized within 30 min after the morphine injection, a diagnosis of acute cholecystitis was made. If the patient was allergic or could not tolerate intravenous morphine, a delayed image was taken at 3 h after the tracer injection with the same dichotomous interpretation. If there was liver visualization, but no biliary tract or gut visualization at 60 min after the tracer injection, the test was aborted, and the patient was given the diagnosis of acute common bile duct obstruction or marked hepatocellular disease depending on the degree of tracer clearance from the cardiac blood pool and ancillary laboratory information.

The histopathologic findings obtained included the presence and number of stones, gallbladder wall thickness in millimeters, gallbladder structure (e.g., necrosis, gangrene, and hemorrhage) after dehydration with formaldehyde, and the overall diagnosis of cholecystitis based on transmural leukocyte infiltrates. Histologically positive acute cholecystitis was determined by the pathologist's interpretation as acute cholecystitis, or acute on chronic cholecystitis, or the presence of gangrene and necrosis. Intraoperative positive acute cholecystitis was determined by the surgeon's impression based on the intraoperative appearance of the gallbladder and its surrounding tissues. Patients with true positive acute cholecystitis were defined as those who had histologic findings suggestive of acute cholecystitis. Patients were considered true negative for acute cholecystitis if they had a cholecystectomy with histologic findings other than acute cholecystitis, including chronic cholecystitis, cholelithiasis, cholesterolosis, and normal gallbladder.

2.2. *Statistical analysis*

Data were gathered by three trained, nonblinded nurse practitioners and entered into a Microsoft Excel spreadsheet according to the deidentified codes prepared. The data collectors were not assessed for inter-rater reliability and unresolved data points, or obvious entry errors were reviewed by the principal investigator (C.K.) and clarified.

For normally distributed variables, such as age and mean ± standard deviation (SD), were displayed, and groups were compared using a one-way analysis of variance. For skewed variables, such as hours to first test or hours to surgery, means and 25th/75th percentiles were displayed, and groups were compared using a nonparametric Kruskal–Wallis test. Categorical variables, such as gender, were displayed using frequency (*N*) and percent, and a Pearson chi-square test was used to compare across groups.

The percent of patients who had each AUS finding (stones, sludge, Murphy sign, gallbladder distension, pericholecystic fluid, and gallbladder wall thickening) was compared for histologically proven acute cholecystitis *versus* histologically proven nonacute cholecystitis cases using Pearson chi-square test. The total number of AUS signs was computed as the total number of signs present within an individual case. The relationship of the total number of signs present to histologically proven acute cholecystitis was assessed through a logistic regression model, as was the relationship of each AUS results category ("acute cholecystitis" or "likely or equivocal acute cholecystitis" *versus* "nonacute or undetermined") for predicting histologically proven acute cholecystitis and intraoperative findings of acute cholecystitis. The percent of patients who had a diagnosis of acute cholecystitis histopathologically was compared with the percent of patients who had a diagnosis of acute cholecystitis intraoperatively for each combined test result using McNemar test of symmetry, using an exact *P* value due to small numbers of cases in some categories.

The sensitivity of AUS and HIDA scan was calculated as the percentage of true positive (i.e., histopathologically positive or intraoperatively positive) cases that were assessed as positive using their respective preoperative imaging modality. The combined sensitivity of AUS and HIDA scans was calculated for cases when both tests were performed, as the percentage of true positive cases that were positive by either AUS or HIDA scan or both AUS and HIDA scan. The performance of the AUS and HIDA tests were compared for cases that had both tests, using McNemar test of symmetry. The 95% confidence intervals (CIs) for sensitivity were based on the binomial distribution. All hypothesis tests were carried out using a significance level of 0.05. Data analysis was performed using SAS 9.3 software for Windows (SAS Institute, Cary, NC).

3. Results

A total of 9087 emergency room visit charts were retrospectively reviewed, with 406 patients who underwent cholecystectomy meeting inclusion criteria for this study. One hundred thirty-two (32.5%) patients had AUS only, 46 (11.3%) patients had HIDA scan only, and 228 (56.2%) patients had both AUS and HIDA scan. The average age of patients was 49.4 ± 18.5 y.

Patients who underwent only HIDA scan were somewhat, but not significantly, older than patients who received only AUS or both AUS and HIDA scan ($P = 0.09$). Overall, female patients predominated with 270 women (66.5%) and 136 men (33.5%) in the total study group. The percentage of women did not differ significantly across imaging modalities ($P = 0.09$). The median time (25th/75th percentile) from admission to first imaging study for all patients was 2.5 h (1.5/4.5 h). Median hours from admission to first imaging study differed significantly across imaging modalities ($P < 0.01$) with patients receiving only HIDA scan having longer median time from admission to their first imaging study (8.0 h) than patients with only AUS (2.5 h) or both AUS and HIDA scan (2.0 h). Median time (25th/75th percentile) from admission to surgery was 15.0 h (11.0 h/27.0 h) for all patients and did not differ significantly across imaging modalities ($P = 0.40$). Among the 228 patients who had both AUS and HIDA scan, AUS was the initial investigation for 215 (94.3%) patients, HIDA scan was performed first for 11 (4.8%) patients, 1 patient (0.4%) had AUS and HIDA scan times recorded as the same, and the HIDA scan time was missing for 1 patient (0.4%). Table 1 shows the characteristics of patients for each imaging modality.

Among the 360 patients with AUS performed, 330 (91.7%) had gallstones, 102 (28.3%) were positive for sludge, 149 (41.4%) had positive sonographic Murphy sign, 69 (19.2%) had gallbladder distension, 65 (18.1%) had pericholecystic fluid, and 48 (13.3%) had gallbladder wall thickening (gallbladder wall thickness ≥5 mm). Thickness of the gallbladder wall was reported for 95 of the 360 cases (26.4%). The average thickness was 4.9 ± 2.0 mm and ranged from 1 to 17 mm. The percentage of patients with stones, sludge, or pericholecystic fluid did not differ significantly among the histologically proven acute and nonacute cholecystitis cases. However, there was a significant difference in the percentage of patients who had sonographic Murphy sign between the histologically proven acute and nonacute cholecystitis cases (47.1% *versus* 35.3%, $P = 0.02$), among patients who had gallbladder distension (23.5% *versus* 14.5%, $P = 0.02$), and among patients with gallbladder wall thickening (17.7% *versus* 8.7%, $P = 0.01$). The total number of AUS findings present ranged from 0 to 6 (mean = 2.1, SD = 1.1). Although there was not a large difference in the mean number of AUS findings for histologically confirmed acute cholecystitis cases when compared with histologically proven nonacute cholecystitis cases (mean = 2.3, SD = 1.1 *versus* mean = 1.9, SD = 1.1, respectively), this difference was significant ($P = 0.01$). The AUS findings and their relationship to histologic diagnosis are summarized in Table 2.

Table 1 – Comparison of preoperative characteristics of 406 cholecystectomy patients for those who had AUS only, HIDA scan only, and both diagnostic imaging modalities.

Preoperative characteristics	All patients (N = 406)	AUS only (N = 132)	HIDA scan only (N = 46)	AUS + HIDA scan (N = 228)	P value*
Age, mean ± SD	49.4 ± 18.5	50.0 ± 19.0	54.4 ± 20.4	48.0 ± 17.6	0.09†
Female, N (%)	270 (66.5%)	91 (68.9%)	24 (52.2%)	155 (68.0%)	0.09‡
Hours to first imaging study, median (25th/75th percentile)	2.5 (1.5/4.5)	2.5 (1.5/4.0)	8.0 (5.0/11.0)	2.0 (1.0/4.0)§	<0.01‖
Hours to surgery, median (25th/75th percentile)	15.0 (11.0/27.0)	14.0 (8.0/45.0)	14.8 (12.0/22.0)	16.0 (11.8/23.0)	0.40‖

* P values are for comparison of the three imaging modalities: AUS only, HIDA scan only, and AUS + HIDA scan.
† P value based on one-way analysis of variance.
‡ P value based on Pearson chi-square test.
§ 215 (94.3%) of patients who underwent both AUS and HIDA scan had the AUS done first.
‖ P value based on Kruskal–Wallis nonparametric test.

Preoperative radiologist reports of the 360 AUS cases described 173 (48.1%) as acute cholecystitis, 58 (16.1%) as likely or equivocal acute cholecystitis, and 129 (35.8%) as nonacute or undetermined. Of the 187 patients who were histologically proven acute cholecystitis, the ultrasound report was read as acute cholecystitis in 100 (53.5%) cases, likely or equivocal acute cholecystitis in 37 (19.8%) cases, and nonacute or undetermined in 50 (26.7%) cases. Among the 173 histologically confirmed nonacute cholecystitis cases, the ultrasound report was read as acute cholecystitis in 73 (42.2%) cases, likely or equivocal acute cholecystitis in 21 (12.1%) cases, and nonacute or undetermined in 79 (45.7%) cases. The odds ratios (ORs) of being diagnosed as acute cholecystitis were calculated for cases with an AUS result of "acute cholecystitis" *versus* "nonacute or undetermined" (Odds ratio [OR] = 2.16, $P = 0.01$), and "likely or equivocal cholecystitis" *versus* "nonacute or undetermined" (OR = 2.78, $P < 0.01$). There was no significant difference in the OR of being diagnosed as histologically proven acute cholecystitis for the "acute" AUS group *versus* the "likely or equivocal" AUS group ($P = 0.42$). The relationships of AUS test results to histologic diagnosis are summarized in Table 3.

The preoperative radiological reports for the 274 HIDA scans were assessed as follows: 221 (80.7%) as acute cholecystitis, 14 (5.1%) as partial or complete common bile duct obstruction with inability to visualize the gallbladder, 16 (5.8%) as chronic cholecystitis, 2 (0.7%) as cholelithiasis, 1 (0.4%) as cholesterolosis, and 20 (7.3%) as normal. Preoperative radiologist reports of the 274 HIDA scan cases described 221 (80.7%) as acute cholecystitis, and 53 (19.3%) as nonacute cholecystitis. Of the 156 patients who were histologically proven acute cholecystitis, the HIDA scan report was read as acute cholecystitis in 143 (91.7%) cases, and nonacute cholecystitis in 13 (8.3%) cases. Among the 118 histologically confirmed nonacute cholecystitis cases, the HIDA scan report was read as acute cholecystitis in 78 (66.1%) cases, and nonacute cholecystitis in 40 (33.9%) cases. The odds ratios of being diagnosed as acute cholecystitis were calculated for cases with an HIDA scan result of "acute cholecystitis" *versus* "nonacute cholecystitis" (OR = 5.64, $P < 0.01$). The relationships of HIDA scan results to histologic diagnosis are summarized in Table 3.

Histologic diagnosis of acute cholecystitis was made in 214 (52.7%) of the 406 cholecystectomies, whereas an intraoperative diagnosis of acute cholecystitis was made in 320 (78.8%). There was a significantly higher percentage of positive cases based on intraoperative diagnosis than on histopathologic diagnosis (McNemar test chi-square = 89.2, df = 1, $P < 0.001$).

There were 228 cases that had both AUS and HIDA scan performed. Both imaging studies were negative for acute cholecystitis for 25 cases, and among these 25 cases three of

Table 2 – Number of patients who had each AUS finding analyzed by histologic diagnosis.

Ultrasound findings	All AUS cases (N = 360); N (%)	Histologically acute cholecystitis (N = 187); N (%)	Histologically nonacute cholecystitis (N = 173); N (%)	P value§
Stones	330 (91.7%)	169 (90.4%)	161 (93.1%)	0.36
Sludge	102 (28.3%)	56 (30.0%)	46 (26.6%)	0.48
Sonographic Murphy sign	149 (41.4%)	88 (47.1%)	61 (35.3%)	0.02*
Gallbladder distension	69 (19.2%)	44 (23.5%)	25 (14.5%)	0.03*
Pericholecystic fluid	65 (18.1%)	37 (19.8%)	28 (16.2%)	0.38
Gallbladder wall thickening	48 (13.3%)	33 (17.7%)	15 (8.7%)	0.01*
Number of AUS findings present, mean ± SD	2.1 ± 1.1	2.3 ± 1.1	1.9 ± 1.1	<0.01*,†

* Significant result, P value <0.05.
† P value for number of AUS signs based on a logistic regression model.
§ P value is for the comparison of percentage of patients in each category for histologically acute *versus* nonacute cholecystitis cases, based on Pearson chi-square test.

Table 3 – Number of patients who had each AUS and HIDA scan preoperative radiological reading analyzed by histologic diagnosis, and ORs for predicting acute cholecystitis based on the imaging findings.

Preoperative radiological reading	All AUS cases (total N = 360); N (%)	Histologically acute cholecystitis (total N = 187); N (%)	Histologically nonacute cholecystitis (total N = 173); N (%)	OR (95% CI)**	P value†
AUS reading					
Acute cholecystitis	173 (48.1%)	100 (53.5%)	73 (42.2%)	2.16 (1.36, 3.45)	<0.01‡,*
Likely or equivocal acute cholecystitis	58 (16.1%)	37 (19.8%)	21 (12.1%)	2.78 (1.46, 5.29)	<0.01§,*
Nonacute cholecystitis or undetermined	129 (35.8%)	50 (26.7%)	79 (45.7%)	1.0 (ref)	
	All HIDA scan cases (total N = 274); N (%)	Histologically acute cholecystitis (total N = 156); N (%)	Histologically nonacute cholecystitis (total N = 118); N (%)	OR (95% CI**)‖	
HIDA scan reading					
Acute cholecystitis	221 (80.7%)	143 (91.7%)	78 (66.1%)	5.64 (2.87, 11.18)	<0.01¶,*
Nonacute cholecystitis#	53 (19.3%)	13 (8.3%)	40 (33.9%)	1.0 (ref)	

* Significant result, P value <0.05.
† P values are based on a logistic regression.
‡ P value for AUS test result of "acute cholecystitis" *versus* "nonacute cholecystitis" for predicting histologically proven acute cholecystitis.
§ P value for AUS test result of "likely or equivocal acute cholecystitis" *versus* "nonacute cholecystitis or undetermined" for predicting histologically proven acute cholecystitis.
‖ OR and 95% CI for HIDA scan test result of "acute cholecystitis" *versus* "nonacute cholecystitis" for predicting histologically proven acute cholecystitis.
¶ P value for HIDA scan result of "acute cholecystitis" *versus* "nonacute cholecystitis" for predicting histologically proven acute cholecystitis.
\# Nonacute cholecystitis result for HIDA scan included chronic cholecystitis, cholelithiasis, cholesterolosis, and normal.
** OR and 95% CI for AUS test result of "acute cholecystitis" or "likely or equivocal acute cholecystitis" *versus* "nonacute cholecystitis" for predicting histologically proven acute cholecystitis.

them (12.0%) were found to be acute histologically, whereas 11 of them (44.0%) were found to be acute intraoperatively (McNemar test $P < 0.01$). AUS was positive and HIDA scan was negative for acute cholecystitis for 20 cases, and among these cases five (30.0%) were diagnosed as acute cholecystitis histologically, whereas 11 (55.0%) were diagnosed intraoperatively (McNemar test $P = 0.06$). HIDA scan was positive and AUS was negative for acute cholecystitis for 59 cases, and among these, 38 cases (64.4%) were diagnosed as acute cholecystitis histologically, whereas 54 (89.9%) were diagnosed as acute cholecystitis intraoperatively ($P < 0.01$). Both imaging studies were positive for acute cholecystitis for 124 cases, and among these, 82 (66.1%) were diagnosed as histologically acute, whereas 119 (96.0%) were diagnosed as acute intraoperatively (McNemar test $P < 0.01$). The number and percent of patients who were histologically and intraoperatively diagnosed with acute cholecystitis for each combined test result are shown in Table 4.

When histologically proven acute cholecystitis was used as the "gold standard," the sensitivity of AUS alone was 73.3% (95% CI = 66.3%–79.5%), the sensitivity of HIDA scan alone was 91.7% (95% CI = 86.2%–95.5%), and the sensitivity of AUS and HIDA scan combined was 97.7% (95% CI = 93.4%–99.5%). The HIDA scan had significantly higher sensitivity than the AUS (McNemar test chi-square = 23.3, df = 1, $P < 0.01$). We also found that the sensitivity of AUS plus HIDA scan was significantly improved compared with the sensitivity of AUS alone (McNemar test chi-square = 38.0, df = 1, $P < 0.01$).

When intraoperative diagnosis of acute cholecystitis was used as the diagnostic criterion, the sensitivity of AUS alone was 71.9% (95% CI = 66.3%–77.1%), the sensitivity of HIDA scan alone was 88.1% (95% CI = 83.3%–92.0%), and the sensitivity of AUS and HIDA scan combined was 94.3% (95% CI = 90.1%–97.1%). The sensitivity of AUS only, HIDA scan only, and AUS plus HIDA scan combined for histopathogic diagnosis and intraoperative findings are shown in Table 5.

4. Discussion

Despite being one of the most common surgical diseases, acute cholecystitis remains a vexing problem for Emergency Medicine physicians and General Surgeons, as clinical diagnosis can be incorrect in up to 23% of patients [12]. Accurate diagnosis and treatment in a timely fashion is essential to decrease morbidity and hospitalization costs. AUS and HIDA scan, either alone or in combination, are commonly used to assist in the diagnosis of acute cholecystitis. In our review of 406 patients, 56% who underwent cholecystectomy after presenting to the Emergency Department with acute upper abdominal pain had both AUS and HIDA scan before the surgery. AUS was the only investigation in 33% of the patients, and HIDA scan was the only imaging modality in 11% of the patients. These results indicate a lack of consistency in selecting the best diagnostic imaging modality for acute cholecystitis.

Table 4 – Number of patients who had histopathologic and intraoperative diagnosis of acute cholecystitis in each test result category for 228 patients who had both AUS and HIDA scan.

Combined test result	Diagnosis based on:		P value[†]
	Histopathologic diagnosis true positive number positive/total (%)[*]	Intraoperative findings acute cholecystitis number positive/total (%)[*]	
AUS^{-} $HIDA^{-}$ ($n = 25$)	3/25 (12.0%)	11/25 (44.0%)	<0.01
AUS^{+} $HIDA^{-}$ ($n = 20$)	6/20 (30.0%)	11/20 (55.0%)	0.06
$HIDA^{+}$ AUS^{-} ($n = 59$)	38/59 (64.4%)	53/59 (89.8%)	<0.01
AUS^{+} $HIDA^{+}$ ($n = 124$)	82/124 (66.1%)	119/124 (96.0%)	<0.01

[*] Percent of patients in each test result category that were diagnosed as acute cholecystitis.
[†] P value based on McNemar test comparing percent positive acute cholecystitis cases by histopathologic diagnosis *versus* percent positive acute cholecystitis cases by intraoperative finding in each combined test result category.

Over the last four decades, AUS has become known as a quick, noninvasive, and reliable imaging modality to diagnose gallstone disease [13,14]. However, its diagnostic value for the presence of acute cholecystitis remains debatable. The 2013 revised Tokyo Guidelines for acute cholecystitis suggest that after initial clinical evaluation, obtaining an AUS as the first examination is level 1A evidence, although its moderate sensitivity of 50%–88% is well recognized [15]. Other investigators suggest that the combination of right upper quadrant pain, nausea, and abdominal tenderness on clinical examination could have higher sensitivity than an AUS alone [15]. One of the limitations of using AUS in diagnosing acute cholecystitis is its inability to clearly identify cystic duct obstruction. Our results showed that the number of AUS signs suggestive of acute cholecystitis on initial evaluation was higher in patients who had histologically proven acute cholecystitis (mean = 2.3) when compared to those who did not have histologically confirmed inflammation of the gallbladder (mean = 1.9). Although this difference was statistically significant ($P < 0.01$), it may not be clinically relevant. A separate study might be helpful to delineate the clinical importance of this finding.

Alternatively, in patients with suspected acute cholecystitis, several studies have recognized HIDA scan to have a higher sensitivity and accuracy than AUS [7,12]. A HIDA scan can be used to directly show cystic duct obstruction resulting in nonvisualization of the gallbladder, which is the cause of acute cholecystitis. Therefore, HIDA has become a preferred imaging modality in some institutions, with AUS only used to confirm the presence of gallstones or sludge [6]. While using a radioactive tracer, a HIDA scan exposes patients to minimal radiation and is generally considered safe. Besides, in some occasions AUS cannot be completed because of the technical difficulties in obtaining adequate views of the gallbladder, such as uncooperative individuals or patients with large body habitus, which makes HIDA scan a useful alternative imaging modality.

At our institution, initial imaging selection is Emergency Medicine physician and General Surgeon dependent, with 75% of patients undergoing AUS within 4 h of presentation to the Emergency Department, and 94% undergoing AUS as the initial investigation. Numerous reasons may be contributing to this trend such as ultrasound's immediate availability and better accessibility after hours, lower cost, absence of ionizing radiation, and more comprehensive examination of the upper abdominal organs with ability to diagnose pathologic conditions that are not confined to the hepatobiliary tract. Cholestasis does not interfere with the interpretation of the AUS

Table 5 – Sensitivity of AUS and HIDA scan alone and in combination based on histopathologic diagnosis and intraoperative diagnosis.

Test modality	Histopathologic diagnosis		Intraoperative diagnosis	
	Sensitivity (%)	95% CI	Sensitivity (%)	95% CI
AUS ($N = 360$)	73.3[*]	66.3 to 79.5	71.9[†]	66.3–77.1
HIDA scan ($N = 274$)	91.7[‡]	86.2 to 95.5	88.1[§]	83.3–92.0
AUS plus HIDA scan ($N = 228$)	97.7[‖]	93.4 to 99.5	94.3[¶]	90.1–97.1

[*] Percent of histopathologically proven acute cholecystitis cases with an available AUS test that were positive for acute cholecystitis on AUS (137/187) × 100 = 73.3%.
[†] Percent of intraoperatively diagnosed acute cholecystitis cases with an available AUS test that were positive for acute cholecystitis on AUS (200/278) × 100 = 71.9%.
[‡] Percent of histopathologically proven acute cholecystitis cases with an available HIDA scan test that were positive for acute cholecystitis on HIDA scan (143/156) × 100 = 91.7%.
[§] Percent of intraoperatively diagnosed acute cholecystitis cases with an available HIDA scan test that were positive for acute cholecystitis on HIDA scan (208/236) × 100 = 88.1%.
[‖] Percent of histopathologically proven acute cholecystitis cases with both available AUS and HIDA scan tests that were positive for acute cholecystitis on either test (126/129) × 100 = 97.7%.
[¶] Percent of intraoperatively diagnosed acute cholecystitis cases with both available AUS and HIDA scan tests that were positive for acute cholecystitis on either test (183/194) × 100 = 94.3%.

Table 6 – Major studies in the literature comparing sensitivity of AUS and HIDA scan in patients with suspected acute cholecystitis.

Study; year; country	Number of included patients with imaging	Reference standard	Patient selection criteria	Percentage of AC (*N*)	Sensitivity of AUS *versus* HIDA (%)	Superior diagnostic study
Alobaidi *et al.*; 2004; United States [17]	107	Surgery (107)	Histopathologically confirmed AC	100 (107)	70.4 *versus* 90.9	HIDA
Kalimi *et al.*; 2001; United States [6]	132	Surgery (132)	Histopathologically confirmed AC	74 (97)	48 *versus* 86	HIDA
Chatziioannou *et al.*; 2000; United States [7]	44	Surgery (44)	Histopathologically confirmed AC	57 (25)	40 *versus* 92	HIDA
Lauritsen *et al.*; 1988; Denmark [19]	67	Surgery (41) + FU (26)	Clinical suspicion of AC (criteria defined)	63 (42/67) for HIDA scan and 76 (41/54) for US	91 *versus* 95	HIDA
Gill *et al.*; 1985; United Kingdom [23]	47	Surgery (23) + FU (24)	Clinical suspicion of AC (no criteria defined) and histopathologically confirmed AC for surgical patients	91 (21/23) for US and 83 (19/23) for HIDA scan	91.3 *versus* 100	HIDA
Freitas *et al.*; 1982; United States [12]	192	Surgery (114) + FU (81)	Acute abdominal pain (<72 h), AUS and cholescintigraphy performed	31 (59)	81.4 *versus* 98.3	HIDA
Ralls *et al.*; 1982; United States [20]	59	Surgery (28) + FU (31)	Referred to radiology department with clinical suspicion of AC (no criteria)	47 (28)	85.7 *versus* 85.7	Equivalent
Zeman *et al.*; 1981; United States [22]	144	Surgery (81) + FU (63)	Acute abdominal pain with suspicion of AC (no criteria)	30 (43)	67 *versus* 98	HIDA
Suarez *et al.*; 1980; United States [21]	85	Surgery (67) + FU (18)	Clinical suspicion of acute gallbladder disease (no criteria defined)	52 (44)	86.6 *versus* 98[*]	HIDA
Down *et al.*; 1979; Australia [18]	116	Surgery (63) + FU (54)	Clinical suspicion of AC or biliary colic (no criteria defined)	56 (66)	54 *versus* 99	HIDA

AC = acute cholecystitis; FU = follow up.
[*] Sensitivity was not recorded. The numbers refer to the diagnostic accuracy of the imaging modality.

result as opposed to HIDA scan where cholestasis may interfere with excretion of the agents used and give a false-positive result. A false-positive rate up to 6% for HIDA scan can also be seen in patients with pancreatitis, or patients who have been nothing by mouth for a prolonged period of time [16]. In addition, HIDA scan has other logistic drawbacks that limit its use as the initial modality of choice for clinically suspected acute cholecystitis. It usually takes several hours for the examination to be completed, information is confined to the hepatobiliary tract, and it carries the burden of ionizing radiation.

Our calculations of sensitivity in diagnosing acute cholecystitis based on the histopathologic diagnosis were 73.3% for AUS alone, and 91.7% for HIDA scan alone. We reviewed major published studies over the last 35 y (Table 6) and found a wide range of reported sensitivities for AUS in diagnosing acute cholecystitis from 40% to 91%. [6,7,12,17–23] User dependency, variability in definitions for acute cholecystitis, and technologic improvements over time make a direct comparison difficult, but our sensitivity of 73.3% compares favorably with these results. Our sensitivity for HIDA scan of 91.7% falls well into the reported range of 86%–100%, as expected given the more objective nature of this imaging modality. It is important to note that our study has the largest cohort of patients who underwent both diagnostic workup with imaging, followed by cholecystectomy and histopathologic confirmation when compared with all available studies. In 2012, Kiewiet *et al.* [11] published the largest meta-analysis and calculated the summary estimate of sensitivity for AUS to be 81%, and the summary estimate of sensitivity for HIDA scan to be 96% which was significantly higher than that of ultrasound. Although the summary estimate of sensitivities for both the AUS and HIDA scan were found to be higher in the meta-analysis compared with our calculated sensitivities, an analogous trend was observed indicating that HIDA scan is a more sensitive imaging modality for the diagnosis of acute cholecystitis. Moreover, we demonstrated that the sensitivity in diagnosing acute cholecystitis based on the histopathology was 97.7% for the combined imaging of AUS and HIDA scan. Indeed, our data indicate that the sensitivity significantly improves when HIDA scan is added to the diagnostic work up.

Also, in this study we examined different combinations of ultrasound findings to search for markers of acute cholecystitis based on ultrasound imaging alone. We found that the presence of sonographic Murphy sign, gallbladder distention, and gallbladder wall thickening were significantly associated with histologically proven acute cholecystitis; however, none of these individual findings alone were sufficient to be diagnostic for acute cholecystitis on final pathology. Simply calculating the total number of ultrasound findings present was also a significant predictor of histologically confirmed acute cholecystitis ($P < 0.01$), although the differences are not sufficient to make this a clinically useful tool as a sole diagnostic measure. Previous studies, however, found ultrasound to be helpful in establishing the presence of gallstones [6]. Thus, in patients with known cholelithiasis who present to the Emergency Department with symptomatology suggestive of acute cholecystitis, a repeat AUS may not be as useful a diagnostic tool as an initial HIDA scan.

We also examined the sensitivities of the AUS and HIDA scan in diagnosing acute cholecystitis based on the intraoperative diagnosis made by the operating surgeon. The sensitivities were 71.9% for ultrasound alone, 88.1% for HIDA scan alone, and 94.3% for the combined imaging of AUS and HIDA scan. Intraoperative diagnosis of acute cholecystitis based on gallbladder morphology, and other signs of inflammation was made in a significantly higher proportion of cases than histologically proven acute cholecystitis (78.8% *versus* 52.7%, $P < 0.0001$). This was observed with all four different combinations of the two imaging modalities. Whether this observation represents a lack of sensitivity of histopathology for a diagnosis of acute cholecystitis, or overdiagnosis of acute cholecystitis based on intraoperative findings cannot be determined from our data.

A number of limitations of this study warrant discussion and should be taken into consideration. As a retrospective review, our study lacks the ability to prove cause and effect. A randomized controlled trial, however, would be logistically and ethically challenging, as patients with nonspecific complaint of upper abdominal pain could not safely be randomized to AUS or HIDA scan, when other imaging modalities, such as computed tomography, may be more appropriate based on clinical presentation. Selection bias was present because clinicians, either Emergency Department physicians or General Surgeons, chose the imaging modality based on personal choice or patient history of biliary colic. In addition, AUS are performed by sonographers with varying degrees of experience, which introduces variability in the quality of the examination. For instance, the technician's ability to elicit sonographic Murphy sign varies and depends on several factors, including patient cooperation. Also, the actual technique of the AUS is operator dependent, whereas the HIDA injection and imaging technique is less dependent on operator differences.

5. Conclusions

In patients with acute abdominal pain and suspected acute cholecystitis, AUS has limited sensitivity in diagnosing this condition. The addition of a HIDA scan significantly improves sensitivity for the diagnosis of acute cholecystitis and allows for the detection of almost all cases of acute cholecystitis. In equivocal cases, pursuing further workup for suspected acute cholecystitis with a HIDA scan can add valuable information.

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