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Authors

Villar, Julian
Summers, Shane M
Menchine, Michael D
et al.

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Ultrasound in Emergency Medicine

THE ABSENCE OF GALLSTONES ON POINT-OF-CARE ULTRASOUND RULES OUT ACUTE CHOLECYSTITIS

Julian Villar, MD, MPH,* Shane M. Summers, MD, RDMS,† Michael D. Menchine, MD, MPH,†
 J. Christian Fox, MD, RDMS,† and Ralph Wang, MD, RDMS*

*Department of Emergency Medicine, University of California, San Francisco, San Francisco and †Department of Emergency Medicine, University of California, Irvine, Orange, California

Reprint Address: Julian Villar, MD, MPH, Department of Emergency Medicine, University of California, San Francisco, 505 Parnassus Ave, M24, San Francisco, CA 94143

Abstract—Background: Cholelithiasis affects an estimated 20 million people in the United States yearly; 20% of symptomatic patients will develop acute cholecystitis (AC). A recent single-center study estimating test characteristics of point-of-care ultrasonography (POCUS) for the detection of AC, as defined by gallstones plus sonographic Murphy's or pericholecystic fluid or gallbladder wall-thickening, resulted in a sensitivity and specificity of 87% (95% confidence interval [CI] 66–97) and 82% (95% CI 74–88), respectively. No prior studies have been conducted to estimate the test characteristics of POCUS for the purpose of excluding acute calculous cholecystitis. **Objective:** To determine whether the finding of gallstones alone on POCUS has high sensitivity, high negative predictive value, and low negative likelihood ratio for the exclusion of AC. **Methods:** We conducted an analysis using data from a prospective cross-sectional single-center study of POCUS test to estimate the test characteristics using a simplified definition of a positive test – the presence of gallstones alone. **Clinical follow-up and pathology reports** were used as the reference standard. Test characteristics were calculated and compared to the standard definition, gallstones plus one secondary finding. **Results:** The overall prevalence of AC was 14% (23 pathology-confirmed cases of 164 included patients). The sensitivity of the simplified definition was 100% (95% CI 85.7–100), negative predictive value 100% (95% CI 92.2–100), and negative likelihood ratio was < 0.1, compared to a sensitivity of 87% (95% CI 66–97%), negative predictive value 97% (95% CI 93–99%), and negative likelihood ratio of 0.16 (95% CI 0.06–0.5).

Conclusion: Simplifying the definition of the test findings on POCUS to gallstones alone has excellent sensitivity and negative predictive value for the exclusion of AC. This finding, if broadly validated prospectively, confirms the practice of excluding acute calculous cholecystitis using POCUS in emergency department patients. © 2015 Elsevier Inc.

Keywords—cholelithiasis; acute cholecystitis; emergency ultrasound; screening; abdominal imaging

INTRODUCTION

Cholelithiasis is a highly prevalent condition, with an estimated 20 million people in the United States afflicted yearly (1). Of symptomatic patients, 20% will develop acute cholecystitis (AC), accounting for 3% to 9% of hospital admissions for acute abdominal pain (1–3). Point-of-care ultrasound (POCUS) of the gallbladder traditionally focuses on the detection of gallbladder inflammation and biliary obstruction, using the presence of gallstones plus secondary signs, including increased wall thickness > 3 mm, pericholecystic fluid, and sonographic Murphy's sign (4). The addition of a secondary sign in the definition of a positive test is important to increase the specificity of the study to accurately identify those with gallbladder inflammation. A recent prospective study by Summers et al. estimated the test

characteristics of POCUS for the diagnosis of AC, using this traditional definition of a positive test (5). When compared to the pathological reference standard, the traditional definition yielded a sensitivity and specificity of 87% (95% confidence interval [CI] 66–97) and 82% (95% CI 74–88), respectively, and had similar test characteristics to radiology-performed ultrasound (5).

It would be desirable to use POCUS as a screening test to exclude the diagnosis of acute cholecystitis rather than to rule in the diagnosis. Summers et al. reported a negative predictive value of 97% (95% CI 93–99%) and negative likelihood ratio of 0.16 (95% CI 0.06–0.5), which would suggest this as a reasonable approach (5). Prior studies of POCUS of the gallbladder have demonstrated a more modest sensitivity for AC (6–9). In a recent systematic review of point-of-care ultrasound for gallstones, the authors suggest that “a negative emergency ultrasonography result for gallstones ... implies that the emergency physician should consider another diagnosis” (10,11). However, the approach of using POCUS to exclude acute calculous cholecystitis has not been directly assessed.

We sought to estimate the test characteristics of a more simple definition of a positive test, gallstones alone, on POCUS for the presence of acute cholecystitis. We re-analyzed data from a previously published, prospective, cross-sectional study of POCUS for acute cholecystitis. We hypothesized that using a simplified definition would result in superior sensitivity, negative predictive value, and negative likelihood ratio, as compared to gallstones and the presence of a secondary sign. This would confirm the value of the POCUS as a screening test to exclude acute calculous cholecystitis.

MATERIALS AND METHODS

Study Design

We analyzed data previously collected in a prospective, cross-sectional, single-center study. Assessment of POCUS of the gallbladder for AC, as defined by gallstones plus at least one secondary sign, including sonographic Murphy’s sign, pericholecystic fluid, or gallbladder wall thickness > 3 mm, as compared to radiology-performed ultrasound, and to histopathology as the reference standard, was previously conducted. For the current study, we determined the test characteristics of POCUS when the presence of gallstones alone was considered a positive test. The study received Institutional Review Board approval.

Setting

The setting, participant selection, and interventions were previously described (5). Briefly, the study was conducted in an urban university hospital emergency department

(ED), with an annual patient census of 36,000, that supports both an emergency medicine residency-training program and an ultrasound fellowship.

Selection of Participants

A convenience sample of adult patients during business hours between May 2006 and February 2008 were enrolled. Patients 18 years or older who presented to the ED with suspected cholecystitis (right upper quadrant or epigastric pain, vomiting, or fever) were included. Subjects with risk factors for acalculous cholecystitis were not excluded.

Interventions

All subjects underwent POCUS of the gallbladder by the treating physician (attending physicians, ultrasound fellows, or residents), according to their usual practice. Of the 21 faculty, 10 are registered diagnostic medical sonographers (RDMS) certified in abdominal ultrasound. Emergency Medicine residents are required to complete 150 supervised biliary ultrasounds prior to graduation.

For the present analysis we defined POCUS as positive if gallstones were visualized, and negative if no gallstones were visualized. Secondary indicators of AC were ignored. The physicians were blinded to subsequent radiology ultrasound.

Clinical follow-up included phone calls and medical record review to identify patients who underwent a cholecystectomy within 2 weeks of the index visit. Operative and pathology reports were also reviewed as the reference standard for AC.

Outcomes

Patients were classified as positive for AC if they required a cholecystectomy during the index visit or within 2 weeks, and the pathology report was positive. Patients were classified as negative for AC if they had a negative pathology report, never underwent cholecystectomy, or if they underwent a cholecystectomy more than 2 weeks after the index visit. Cases in which pathology reported absence of gallstones, or choledocolithiasis, or cholelithiasis without cholecystitis, were also analyzed as negative.

Statistical Analysis

Primary data from the original study were obtained. Test characteristics of a simplified definition of a positive test were computed with conventional diagnostic test statistics and compared to the previously published test characteristics. Exact binomial distribution CIs were calculated for sensitivity, specificity, positive and negative predictive

values, positive and negative likelihood ratios, and Cohen's Kappa statistic for interrater reliability using the online biostatistics calculator OpenEpi (Openepi.com).

RESULTS

Characteristics of Study Subjects

The characteristics of the study subjects have been described previously. Briefly, 193 of 196 potential subjects were enrolled, with the remaining 3 declining participation. Two patients did not have POCUS performed; 2 patients had ultrasound performed only by medical students without supervision; 23 were lost to follow-up; and 2 had unavailable pathology reports. Thus, 164 patients were included in the final analysis. Forty-nine patients did not have ultrasound performed by radiology, leaving 115 patients included in the interrater reliability portion of the analysis. Demographic characteristics of the study population have been reported previously (5).

Twenty-six patients underwent emergent cholecystectomy; 23 had pathology-confirmed AC (14% prevalence). Of the 3 remaining patients, one had surgical pathology that showed cholelithiasis only, and was classified as negative. No pathology reports were available for the other 2 patients, who were therefore excluded.

Twenty-three of the patients were discharged home after the index ED visit could not be reached by phone and were excluded. Medical record review of these patients did not reveal evidence of admission to the hospital, surgical intervention, or a diagnosis of AC. One hundred forty patients were contacted by phone; one had undergone an elective cholecystectomy more than 2 weeks after the index visit, and was classified as negative.

Main Results

The overall prevalence of AC was 14% (23 confirmed cases of 164 patients). All 23 cases of AC were correctly identified by visualization of gallstones by POCUS. Seventy-seven patients had POCUS negative for gallstones; none were diagnosed with cholecystitis (Table 1). A total of 87 patients had gallstones visualized on POCUS (53% of the patients included in the final analysis).

Sixty-one patients had at least one secondary sign of cholecystitis. Of the 23 patients that were found to have AC on surgical pathology, none had secondary signs but no gallstones. A total of 15 patients had at least one secondary sign of cholecystitis but no gallstones on POCUS. None of these had AC on surgical pathology.

The test characteristics of POCUS for AC using gallstones alone had a sensitivity of 100% (95% CI 85.7–100%), specificity of 54.6% (95% CI 46.8–62.6%), negative predictive value of 100% (95% CI

92.2–100%), and positive predictive value 26.4% (95% CI 18.3–36.6). The negative likelihood ratio was calculated: < 0.01 . The test characteristics of the simplified vs. standard protocol are shown in Table 1.

The kappa statistic for agreement between POCUS and radiology ultrasound for the detection of gallstones was 0.74 (95% CI 0.56–0.93), indicating substantial agreement.

DISCUSSION

In a re-analysis of a prior study of the diagnostic test characteristics of POCUS for acute cholecystitis, we found that using a simplified definition of a positive test (gallstones alone) resulted in a sensitivity of 100% (95% CI 85.7–100%) and a specificity of 54.6% (95% CI 46.8–62.6%). Furthermore, the negative predictive value and negative likelihood ratio for acute cholecystitis of this simplified protocol were calculated to be 100% and < 0.01 , respectively. The main strengths of the original study include a prospective, cross-sectional design, and a clinical gold standard. Our results suggest that emergency physicians could use POCUS to reliably exclude acute calculous cholecystitis in patients with suspected acute cholecystitis.

Prior studies of POCUS have assessed whether emergency physicians can accurately detect gallstones as well as acute cholecystitis, mainly compared to a reference standard of radiology ultrasound (6,7,9,10). In these studies the definition of the POCUS test for acute cholecystitis includes gallstones plus a secondary finding. By including the requirement of a secondary finding, the test becomes more specific, and therefore more valuable for identifying or ruling in acute cholecystitis. However, this also resulted in decreased sensitivity, negative predictive value, and negative likelihood ratio, which decreases the value of the test for excluding or ruling out acute cholecystitis. In our re-analysis, the test characteristics of the simplified definition had a superior sensitivity, negative predictive value, and negative likelihood ratio compared to the standard definition, which indicate that POCUS can be used as a screening test to exclude acute cholecystitis. The present study adds to what is known by comparing the POCUS test finding of gallstones to a histopathological diagnosis of acute cholecystitis and explicitly evaluating whether a simplified definition is superior to the standard definition for excluding acute calculous cholecystitis. We believe that in the presence of gallstones on POCUS, secondary signs should still be used to identify acute calculous cholecystitis, but that the absence of gallstone alone more reliably excludes acute calculous cholecystitis.

Table 1. 2 × 2 Contingency Tables for Acute Cholecystitis (n = 164) by EUS for Gallstones Alone vs. Gallstones Plus Secondary Findings Compared to the Criterion Standard and Test Characteristics of Gallstones Alone vs. Gallstones Plus Secondary Findings Compared to the Criterion Standard

EUS	Gall Stones Alone		Gall Stones + Secondary Signs	
	Acute Cholecystitis	No Acute Cholecystitis	Acute Cholecystitis	No Acute Cholecystitis
Positive	23	64	20	26
Negative	0	77	3	115
Test Characteristic	Value	95% CI	Value	95% CI
Sensitivity, %	100.0	(86–100)	87	(66–97)
Specificity, %	54.6	(46–63)	82	(74–88)
LR+	2.2	(1.8–2.6)	4.7	(3.2–6.9)
LR–	–	–	0.16	(0.06–0.5)
NPV, %	100.0	(95–100)	97	(93–99)
PPV, %	26.4	(18–37)	44	(29–59)

EUS = emergency ultrasound; CI = confidence interval; LR = likelihood ratio; NPV = negative predictive value; PPV = positive predictive value.

Prevalence 14.0%.

Limitations

The current analysis is limited, as the original study was not conducted with the intention to examine the test characteristics of POCUS using gallstones alone. We undertook a secondary analysis of a previously collected data set to test an important hypothesis. However, all patients included in the analysis of the original study had complete data for the variables being analyzed in this study. As such, we do not believe that the post hoc nature of the current analysis is a significant limitation.

The second limitation is the single-center nature of the original study. The physicians participating in this study are highly trained sonologists. The residents are required to complete 150 supervised gallbladder scans prior to graduation, in contrast to the 25 examinations per application recommended by the American College of Emergency Physicians. Furthermore, approximately half of the supervising attendings had obtained RDMS credentials. These results may not be generalizable to all EDs.

As our study specifically targeted the presence or absence of gallstones, its findings cannot be used to evaluate for acalculous cholecystitis. By definition, the absence of gallstones cannot exclude acalculous cholecystitis. However, only 1–5% of all cases of cholecystitis are acalculous, and the disease is typically encountered in the inpatient and intensive care unit setting, rather than the ambulatory care setting (12). Risk factors for gallbladder ischemia and acalculous cholecystitis include trauma, mechanical ventilation, hyperalimentation, post-operative state, diabetes mellitus, vascular insufficiency, prolonged fasting, burns, and postpartum state (13,14). Although we are unaware of evidence that provides

estimates of the prevalence or incidence of acalculous cholecystitis in the Emergency Medicine literature, we suspect that it is lower than 5–10 percent. We have found only case reports of acalculous cholecystitis diagnosed in the ED (15). The most recent American College of Emergency Physicians emergency ultrasound policy statement reports that gallstones are absent in 1–5% of cases of acute cholecystitis (4). Summers et al. enrolled ED patients with right upper quadrant abdominal pain, epigastric pain, vomiting, or fever, who an emergency physician suspected of experiencing acute cholecystitis (5). The only exclusion criteria were those lost to follow-up or with missing pathology reports. No cases of acalculous cholecystitis were identified on radiology ultrasound (0/125, 95% CI 0–2.9%), and none were found on surgical pathology. Therefore, we believe that acalculous cholecystitis is rare in the ED setting, and patients would present with identifiable risk factors. In these patients, the diagnosis of acalculous cholecystitis should be considered and additional imaging should be obtained. This strategy in which POCUS is limited to patients without risk factors for acalculous disease is analogous to the use of POCUS for the evaluation of ectopic pregnancy: the presence of an intrauterine pregnancy on POCUS effectively rules out ectopic for most women, because the frequency of heterotopic pregnancy is very small. However, in patients undergoing in vitro fertilization and other forms of assisted reproduction, where the frequency of the otherwise rare diagnosis of heterotopic pregnancy is higher, radiology imaging should be obtained. We believe that the approach we propose is appropriate in patients that do not have risk factors for acalculous cholecystitis.

CONCLUSION

These findings suggest that using a simplified definition may be adopted as a screening test for AC, and that a negative test safely excludes the diagnosis of AC, with the caveat that it should not be used in patients with certain risk factors for acalculous cholecystitis. To improve the precision and certainty of the estimates, this study should be prospectively validated in a multi-center setting. If validated, emergency physicians could use POCUS of the gallbladder as a simple, noninvasive, point-of-care test to exclude AC in ambulatory patients, potentially resulting in decreased cost, resource utilization, and decreased ED length of stay (16).

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ARTICLE SUMMARY

1. Why is the topic important?

As ultrasound use in the emergency department becomes more widespread, it is imperative that we continue to refine our approach and ensure that the conclusions we derive from our images are supported by evidence.

2. What does this study attempt to show?

This study attempts to show that in healthy, ambulatory patients, the absence of gallstones on emergency ultrasound can be used to help exclude acute cholecystitis (AC) from the differential.

3. What are the key findings?

The test characteristics of emergency ultrasound for AC using gallstones alone had a sensitivity of 100% (95% confidence interval [CI] 85.7–100%), specificity of 54.6% (95% CI 46.8–62.6%), negative predictive value of 100% (95% CI 92.2–100%), and positive predictive value of 26.4% (95% CI 18.3–36.6).

4. How is patient care impacted?

Patient care may be impacted by increasing diagnostic efficiency and reducing length of stay. Point-of-care ultrasound has also been demonstrated to have substantial agreement with radiology ultrasound for the finding of gallstones, but only fair-to-moderate agreement for the secondary signs.