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Research article

Sestamibi as an alternative to mebrofenin for the diagnosis of acute cholecystitis: An alternative option during supply chain disruption☆

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A B S T R A C T

Purpose: To determine the accuracy of Tc-99 m sestamibi for the diagnosis of acute cholecystitis during a supply chain disruption of mebrofenin.
Material and methods: During a national shortage of Tc-99 m mebrofenin in 2019, our institution initiated sestamibi imaging for suspected cases of acute cholecystitis using a standard hepatobiliary imaging protocol. Forty-one patients underwent hepatobiliary imaging with sestamibi, 39 to assess for acute cholecystitis. The examinations were initially interpreted by one nuclear medicine physician and subsequently overread by 5 blinded nuclear medicine physicians (8–30 years' experience). SPECT/CT was obtained for 8 of these patients at the discretion of the primary interpreter. An additional 23 asymptomatic patients (6 with prior cholecystectomy) underwent abdominal scintigraphy as a negative control to determine the normal time to sestamibi accumulation in the gallbladder. A composite reference standard was used (chart review by 3 physicians). Sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values were calculated with and without SPECT/CT (mean ± 95%CI).
Results: Of 39 symptomatic patients, 17/39 had acute cholecystitis and 22 did not. The sensitivity, specificity, PPV and NPV for acute cholecystitis at planar imaging were 97.6 ± 4.6, 62.7 ± 5.2, 67.0 ± 3.6, and 97.3 ± 5.2 % (N = 39). The values changed to 95.7 ± 4.7, 77.9 ± 4.7, 72.1 ± 4.1, and 97.0 ± 3.3 % when control patients were included (N = 62). With SPECT/CT, these mildly improved to 98.8 ± 2.3 %, 69.1 ± 4.4 %, 71.3 ± 3.2 %, and 98.7 ± 2.6 % (N = 39), but not significantly different. On average, sestamibi activity was detected in the gallbladder in negative controls within 1 h.
Conclusion: Tc-99 m sestamibi has excellent sensitivity and NPV for diagnosing acute cholecystitis and can serve as an alternative when mebrofenin is unavailable for evaluating cystic duct obstruction during shortages of standard agents.

1. Introduction

Acute cholecystitis affects approximately 200,000 patients in the United States every year and is the most common clinical indication for hepatobiliary scintigraphy [1,2]. Acute cholecystitis can be diagnosed with other imaging modalities such as CT, MRI, ultrasound, or composite clinical judgment, but hepatobiliary scintigraphy has higher accuracy than other imaging modalities: sensitivity (SN) > 96 % and specificity (SP) of >90 % compared to ultrasound (SN: 81 %, SP: 83 %), CT (SN: 94 %, SP: 59 %), or MRI (SN: 88 %, SP 89 %) [1,3]. Quick and accurate diagnosis of acute cholecystitis enables early treatment (within 72 h of admission) and is

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associated with fewer postoperative complications, shorter hospital length of stay, lower hospital costs, and decreased mortality [1].

Iminodiacetic agents, discovered in the 1980s, are used in hepatobiliary imaging. These agents have prompt hepatic uptake and subsequent excretion into the biliary system. There are two hepatobiliary-agents currently approved by the FDA for hepatobiliary imaging: Tc-99 m disofenin (diisopropyl-IDA [Hepatolite; Pharmalucence]) and Tc-99 m mebrofenin (bromotriethyl-IDA [Choletec; Bracco]). Of the two agents, Tc-99 m mebrofenin (mebrofenin) is preferred due to its increased hepatic extraction (98 % vs 89 %), fast biliary excretion (half-life: 17 min vs 19 min), and greater resistance to displacement by elevated serum bilirubin [2,4,5].

From July 2021 to September 2021, during the COVID-19 pandemic, supply chain disruptions resulted in the temporary unavailability of hepatobiliary agents for hepatobiliary imaging. As a tertiary care center, we perform upwards of ~7–8 hepatobiliary scans per week for acute cholecystitis and was given less than a month notice for the shortage. As we made plans to ration non urgent hepatobiliary scans as we were looking for other nuclear medicine options. At our institution we use Tc-99 m sestamibi for parathyroid and cardiac imaging. Given one of the main methods of elimination for sestamibi is hepatobiliary excretion [6], we thought of this as a potential substitute. Although limited, a review of the literature demonstrated the ability of Tc-99 m sestamibi to incidentally diagnose acute cholecystitis in incidental case [7–12], use in evaluating gallbladder ejection fraction [13–15], and biliary atresia [6]. Thus, it was decided to use Tc-99 m sestamibi clinically for the workup of acute cholecystitis at the authors' institution during the national hepatobiliary shortage. We hypothesized that Tc-99 m sestamibi would have similar diagnostic accuracy to standard of care Tc-99 m mebrofenin. This study is a retrospective analysis of those patients that used Tc-99 m sestamibi for hepatobiliary imaging and presents the diagnostic accuracy of those studies in combination with our best available negative controls, abdominal imaging of asymptomatic patients whose primary indication was parathyroid imaging utilizing Tc-99 m sestamibi.

2. Methods

2.1. Ethical declaration

This HIPAA-compliant, retrospective diagnostic accuracy study was approved by the University of Michigan Institutional Review Board (HUM212599) and conducted and reported using the Standards for Reporting Diagnostic Accuracy Studies (STARD) checklist. The IRB waived the need for informed consent.

2.2. Study cohort

The study cohort included all consecutive patients (N = 41) who underwent acute hepatobiliary imaging with Tc-99 m sestamibi at our institution between July and September 2021 during Tc-99 m mebrofenin shortage. One patient was excluded from the study as they did not maintain a fasting state during the exam period. Another patient underwent sestamibi imaging for suspected bile leak and did not meet inclusion criteria for concern of acute cholecystitis. The remaining 39 patients had an indication of suspected acute cholecystitis. A flow chart summarizing patient selection is depicted in Fig. 1.

Study Cohort Protocol: To optimize gallbladder filling, all patients underwent fasting for 4–6 h per the Society of Nuclear Medicine Practice Guideline for Hepatobiliary Scintigraphy [16]. Additionally, all patients fasting for longer than 24 h or receiving opioid analgesics or total parenteral nutrition were given 0.02 μg/kg cholecystokinin (CCK) to empty the gallbladder prior to radiotracer administration to prevent false positives. After adequate patient preparation, an intravenous dose of 370 MBq (10 mCi) sestamibi was administered to initiate the study.

Hepatobiliary Scan Acquisition: All Tc99 m sestamibi imaging was performed in accordance with the existing protocol for Tc99 m

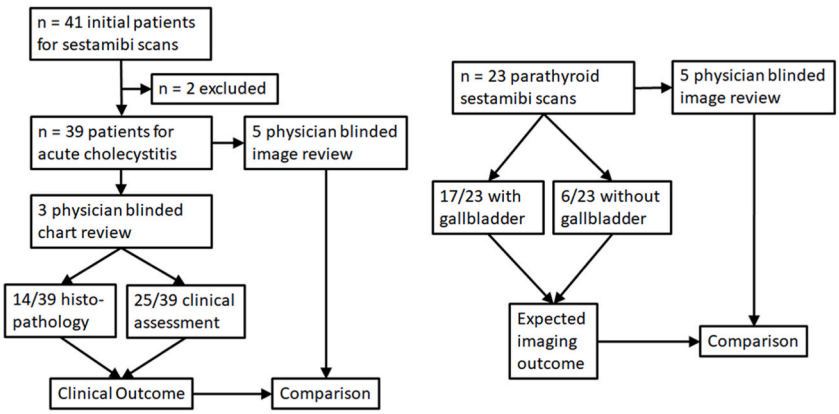

Fig. 1. Flow chart of the study cohort (patients with clinical concern for acute cholecystitis) and control cohort (patients imaged for parathyroid adenoma as a negative control). An initial 41 patients were evaluated with sestamibi. There were 2 patients excluded, 1 for a biliary leak and 1 due to death from COVID and lack of resolution if biliary pathology was present. There were 23 patients that were imaged that were undergoing parathyroid adenoma scan, 6 had their gallbladder previously removed.

mebrofenin imaging. Images were acquired using a large field of view gamma camera with a 128 x 128 matrix and a low-energy high-resolution parallel hole collimator. A dynamic imaging technique was used at a rate of 1 frame per minute for 60 min. These images were obtained in a supine position with the heart and liver in the field of view. Static images were created every 5 min from the summation of previously acquired images. If the gallbladder was visualized by the technologist, a right lateral image was obtained to increase diagnostic confidence. An additional left anterior oblique image was obtained for further detail when the study was performed at the bedside with a portable gamma camera, as SPECT/CT could not be obtained.

The images were then evaluated by the clinical nuclear medicine physician. If the gallbladder was identified by 60 min, no further images were obtained. If the gallbladder was not visualized at 60 min, a 2 mg IV dose of morphine was administered to contract the sphincter of Oddi and encourage filling of the gallbladder. A booster 5 mCi sestamibi dose was also administered if there was not enough radiotracer in the liver parenchyma. Dynamic images were then obtained for 30 more minutes. In patients with a morphine contraindication, morphine was deferred, and delayed imaging was performed at 4 h. If the gallbladder was not visualized 30 min after morphine administration or after 4 h without morphine augmentation, the study was completed. In equivocal cases, SPECT-CT was performed per interpreting physician discretion to improve gallbladder and radiotracer localization.

Image Interpretation: All Tc99 m sestamibi imaging was interpreted in accordance with the existing protocol for Tc99 m mebrofenin imaging. At the conclusion of the study if the gallbladder was not seen after 4 h of imaging or 30 min after morphine administration, then the study was classified as positive for acute cholecystitis. If the gallbladder was visualized within 60 min after radiotracer administration, within 30 min after morphine augmentation, or within 4 h after delayed imaging the study was classified as negative for acute cholecystitis.

During clinical care, a disclaimer was added to the clinical report because the evidence for Tc99 m sestamibi was not yet well established: "Note: Given temporary unavailability of mebrofenin (typically used for hepatobiliary imaging studies), off-label use of sestamibi was employed to assess the biliary system and gallbladder. The hepatobiliary imaging study performed with sestamibi may have reduced specificity and positive predictive value for the identification of cholecystitis compared to mebrofenin, while the negative predictive value is expected to be equally high."

2.3. Control cohort

Given the timeframe of the shortage, the best available control cohort to confirm that Tc99 m sestamibi would work as expected to identify the gallbladder were asymptomatic patients undergoing sestamibi imaging for parathyroid adenoma localization at our institution over a similar period (i.e., August 2021 to September 2021). This group consisted of 23 consecutive patients imaged for parathyroid adenoma localization; six of these patients had previously undergone cholecystectomy (Fig. 1).

Control Cohort Protocol: Unlike the study cohort, the control cohort did not undergo pre-study fasting or other means of gallbladder imaging optimization. Although non ideal as the gallbladder could be stimulated to empty by the mean, patients were asked fast once they arrived. Abdominal imaging was integrated into our standard parathyroid imaging protocol (i.e., SPECT/CT imaging of the head and neck at 30 min and 2 h after injection of 20 mCi sestamibi). The only modification to our standard protocol was injecting the sestamibi while the patient was supine in the camera and acquiring static planar images of the anterior abdomen at 5, 10, 15, 20, 25, and sometimes 30 min. All abdominal planar images were acquired with the same parameters as the study cohort. Additional planar imaging was also obtained at 120 or 150 min depending on availability of the patient and timing of the standard-of-care delayed SPECT/CT scan for imaging their parathyroid. Of the 23 patients that had parathyroid imaging, 3 did not agree to additional abdominal imaging past the 20-min time point. However, the GB was seen in these patients by the 20 min timepoint by all retrospective reviewers, so they remain included in subsequent analysis.

Image Interpretation: After concluding the study, the data was reviewed to determine presence or absence of gallbladder activity. If the gallbladder was visualized, the earliest time point at which the radiotracer was confidently identified within the gallbladder was also obtained.

2.4. Retrospective Image Interpretation

The abdominal Tc99 m sestamibi imaging for all patients was retrospectively reviewed in random order by 5 board-certified nuclear medicine physicians blinded to each other and the chart review "reference standard" of the patient outcome. There was a 3-level image evaluation: a) acute cholecystitis, b) equivocal for cholecystitis, c) negative for acute cholecystitis. Each reader also indicated if they would have ordered SPECT/CT imaging if given the opportunity, and then were shown any available SPECT/CT imaging to repeat their evaluation (this reinterpretation was delayed by 1.5 month and blinded).

2.5. Reference standard

A composite reference standard "truth" was used of the patient's clinical diagnosis. Three physicians (BO, DW, BLV initials) blinded to each other performed independent chart review for all patients. Patients were determined to have acute cholecystitis if 1) surgical pathology confirmed acute cholecystitis, or 2) a clinical diagnosis of acute cholecystitis was made, or 3) a percutaneous cholecystostomy tube was placed. Patients were determined to have no gallbladder if they had imaging showing evidence of a prior cholecystectomy or if there was confirmed history of prior cholecystectomy. Unanimous consent was required and was reached in all cases without adjudication.

2.6. Data analysis

Sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values were calculated with and without SPECT/CT (mean ± 95%CI). Positive imaging results included diagnosis of acute cholecystitis and findings equivocal for acute cholecystitis. Negative imaging results included no evidence of acute cholecystitis. Comparison between groups means was with student t-test assuming significance with a $P < 0.05$.

3. Results

There were 39 evaluable patients in the study cohort (17 had acute cholecystitis and 19 had no cholecystitis based on the reference standard "truth" ie TP or TN) and 23 evaluable patients in the control cohort (0 had acute cholecystitis TN) (Fig. 1). A reference standard was available for all patients in the study cohort (histopathology: 14/39; clinical diagnosis or intervention: 25/39) and control cohort (6/23 with prior cholecystectomy). SPECT/CT was performed on 8/39 patients in the study cohort (21 %) and 0 patients

Table 1
Diagnostic accuracy of Tc-99 m sestamibi for the diagnosis of acute cholecystitis (N = 39 symptomatic patients, N = 23 asymptomatic control patients). Data reflect prospective clinical interpretations (1 reader) and retrospective interpretations (5 blinded readers) stratified by whether the research interpretations had access to SPECT/CT data (N = 8/39 patients) and weather the analysis included asymptomatic control patients (n = 62). No significant difference between prospective reader and retrospective reader in sensitivity or NPV, Specificity and PPV the prospective reader had better performance (*). Evaluation of only symptomatic patients had improved Specificity (** and ***), otherwise presence/absence of control patients had no significant affects in the analysis. Similarly, although SPECT/CT improved the average Sensitivity, Specificity, PPV and NPV it was not significantly different when not taken into consideration ($P < 0.01$ student t-test).

	FP	FN	TP	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	N
All patients, no SPECT/CT for retrospective reads									
Retrospective reader 1	9	3	20	30	**87.0**	**76.9**	**69.0**	**90.9**	62
Retrospective reader 2	7	1	22	32	**95.7**	**82.1**	**75.9**	**97.0**	62
Retrospective reader 3	8	1	22	31	**95.7**	**79.5**	**73.3**	**96.9**	62
Retrospective reader 4	12	0	23	27	**100.0**	**69.2**	**65.7**	**100.0**	62
Retrospective reader 5	7	0	23	32	**100.0**	**82.1**	**76.7**	**100.0**	62
Retrospective reader mean					**95.7**	**77.9****	**72.1**	**97.0**	
Lower 95 % CI of mean					**91.0**	**73.3**	**68.0**	**93.7**	
Upper 95 % CI of mean					***100.0***	**82.6**	**76.2**	***100.0***	
Symptomatic patients, no SPECT/CT for retrospective reads									
Prospective reader	3	0	17	19	**100**	**86.4***	**85.0***	**100**	39
Retrospective reader 1	9	2	15	13	**88.2**	**59.1**	**62.5**	**86.7**	39
Retrospective reader 2	7	0	17	15	**100.0**	**68.2**	**70.8**	**100.0**	39
Retrospective reader 3	8	0	17	14	**100.0**	**63.6**	**68.0**	**100.0**	39
Retrospective reader 4	10	0	17	12	**100.0**	**54.5**	**63.0**	**100.0**	39
Retrospective reader 5	7	0	17	15	**100.0**	**68.2**	**70.8**	**100.0**	39
Retrospective reader mean					**97.6**	**62.7****	**67.0**	**97.3**	
Lower 95 % CI of mean					**93.0**	**57.5**	**63.4**	**92.1**	
Upper 95 % CI of mean					***100.0***	**67.9**	**70.6**	***100.0***	
All patients, SPECT/CT allowed for retrospective reads									
Prospective reader	3	0	23	36	**100**	**92.3**	**88.5***	**100**	62
Retrospective reader 1	8	2	21	31	**91.3**	**79.5**	**72.4**	**93.9**	62
Retrospective reader 2	6	1	22	33	**95.7**	**84.6**	**78.6**	**97.1**	62
Retrospective reader 3	6	1	22	33	**95.7**	**84.6**	**78.6**	**97.1**	62
Retrospective reader 4	10	0	23	29	**100.0**	**74.4**	**69.7**	**100.0**	62
Retrospective reader 5	6	0	23	33	**100.0**	**84.6**	**79.3**	**100.0**	62
Retrospective reader mean					**96.5**	**81.5*****	**75.7**	**97.6**	
Lower 95 % CI of mean					**93.3**	**77.5**	**71.9**	**95.4**	
Upper 95 % CI of mean					**99.7**	**85.6**	**79.5**	**99.8**	
Symptomatic patients, SPECT/CT allowed for retrospective reads									
Prospective reader	3	0	17	19	**100**	**86.4***	**85.0***	**100**	39
Retrospective reader 1	8	1	16	14	**94.1**	**63.6**	**66.7**	**93.3**	39
Retrospective reader 2	6	0	17	16	**100.0**	**72.7**	**73.9**	**100.0**	39
Retrospective reader 3	6	0	17	16	**100.0**	**72.7**	**73.9**	**100.0**	39
Retrospective reader 4	8	0	17	14	**100.0**	**63.6**	**68.0**	**100.0**	39
Retrospective reader 5	6	0	17	16	**100.0**	**72.7**	**73.9**	**100.0**	39
Retrospective reader mean					**98.8**	**69.1*****	**71.3**	**98.7**	
Lower 95 % CI of mean					**96.5**	**64.7**	**68.1**	**96.1**	
Upper 95 % CI of mean					***100.0***	**73.5**	**74.5**	***100.0***	

FP: False positive for acute cholecystitis.
FN: False negative for acute cholecystitis.
TP: True positive for acute cholecystitis.
TN: True negative for acute cholecystitis.

in the control cohort.

The sensitivity, specificity, PPV and NPV for acute cholecystitis at planar imaging were 97.6 ± 4.6 %, 62.7 ± 5.2 %, 67.0 ± 3.6 %, and 97.3 ± 5.2 % (Table 1, Figs. 2 and 3). With the addition of SPECT/CT, these mildly improved to 98.8 ± 2.4 %, 69.1 ± 4.4 %, 71.3 ± 3.2 %, and 98.7 ± 2.6 %, respectively (Fig. 4). The accuracy of the prospective clinical interpretation was 100 %, 92.3 %, 88.5 % and 100 %, respectively. Examples of false positive examinations included cholestasis in severely ill patients and chronic cholecystitis. In some patients with a false positive result no cause could be identified, which was seen in less than 30 % of the cases (Table 1). The retrospective readers stated they would have requested a SPECT/CT in 0 %–38 % of the study cohort patients if they were assigned during routine clinical care (0 %, 38 %, 28 %, 25 %, 22 %) in line with interpreting physician at 21 %.

On average, sestamibi was detected in the gallbladder in negative controls within 1 h (mean 54 min, median 24 min; range: 15–150

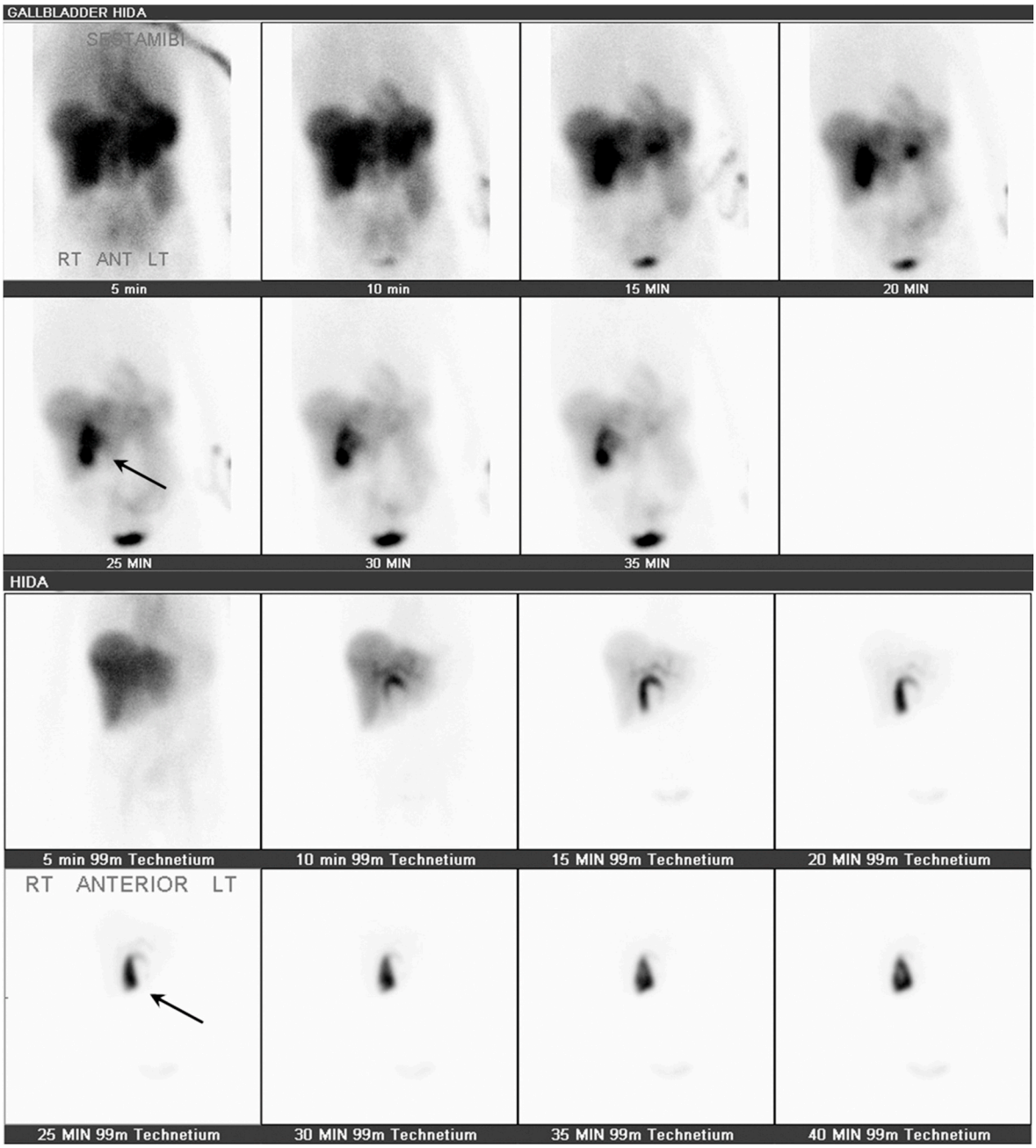

Fig. 2. 37-year-old female with history of acute on chronic abdominal pain admitted for concern of acute cholecystitis. Initial sestamibi scan interpreted as negative as the gallbladder was visualized (arrow). Subsequent repeat imaging with mebrofenin was performed given ongoing clinical concern also negative for acute cholecystitis, which was also normal.

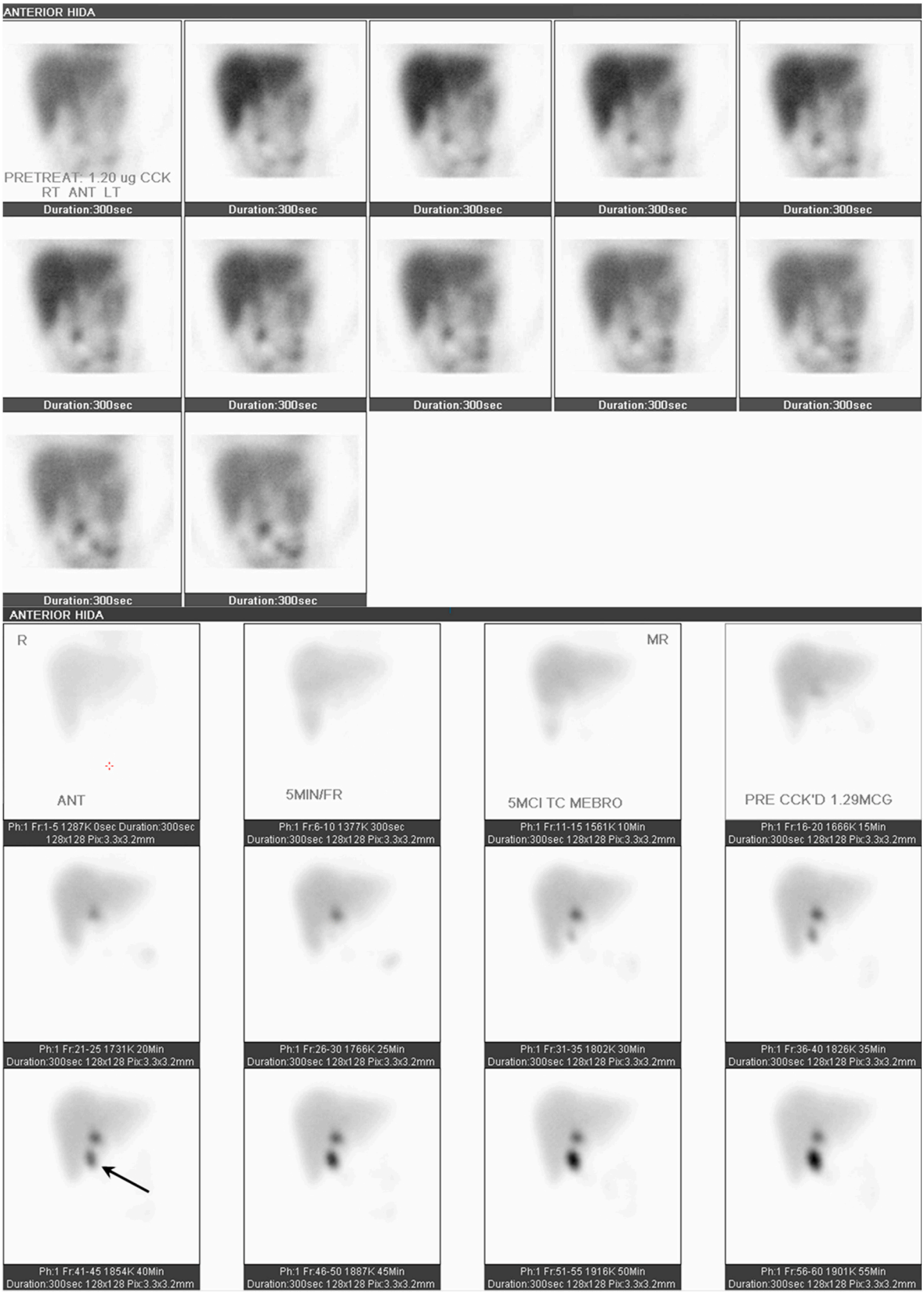

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Fig. 3. 31-year-old female admitted for COVID at 31 weeks pregnant in March. Subsequent delivery, but prolong critical illness with concern for possible acute cholecystitis. Imaging in June with mebrofenin was negative (gallbladder seen arrow). However, further clinical decline and laboratory abnormalities imaging was repeated in July (sestamibi) which was positive. Clinical diagnosis was acalculous cholecystitis given prolong critical illness. Patient died from COVID ARDS related complications. Note prolong tracer uptake in the liver in both studies (compared to Fig. 2) given the underling hepatocellular disfunction consistent from prolong critical illness.

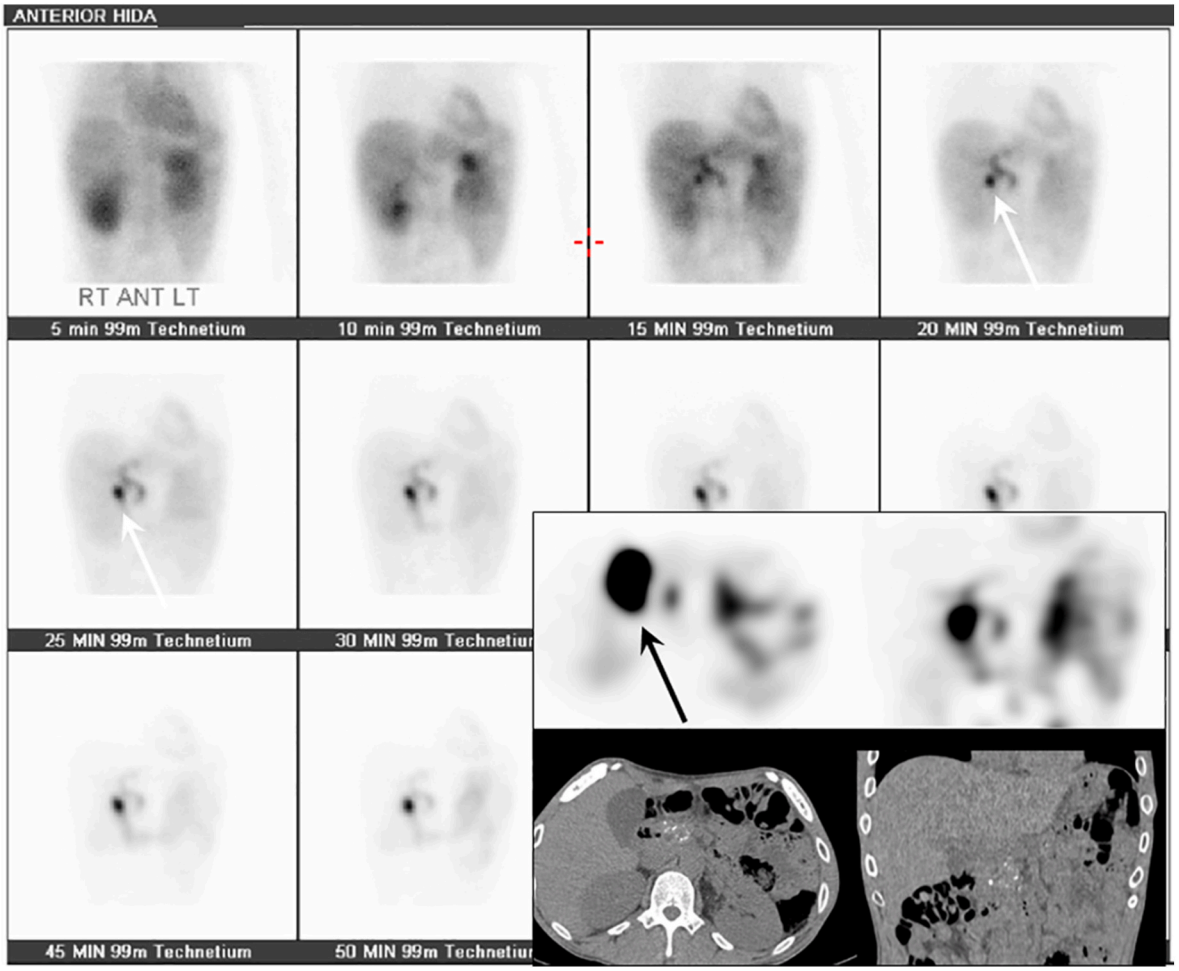

Fig. 4. 44 yo male with history of alcohol abuse and chronic pancreatitis presents with RUQ pain different then his chronic pancreatitis. Sestamibi HEPATBILARY scan for concern of acute cholecystitis is shown. The interpreting physician was unsure if the gallbladder was visualized, white arrow at 20/25 min. Consequently, SPECT/CT was performed demonstrating tracer within the gallbladder, black arrow on axial SPECT image.

min).

4. Discussion

The purpose of this study was to determine the diagnostic accuracy of Tc-99 m sestamibi for the diagnosis of acute cholecystitis in the setting of a mebrofenin supply chain disruption. This retrospective study demonstrated that Tc-99 m sestamibi has high sensitivity (97–99 %) and high negative predictive value (97–99 %) for the diagnosis of acute cholecystitis, but only modest specificity (63–69 %) and positive predictive value (67–71 %). These data imply that Tc-99 m sestamibi can be used to exclude a diagnosis of acute cholecystitis, but there may be more false positive examinations than with mebrofenin (sensitivity and specificity of mebrofenin are reported to be >96 % and >90 %, respectively) [1,3]. There were fewer false positive examinations for the prospective clinical interpretations compared the retrospective readers, which was significant for Specificity and PPV (Table 1). A specific cause is difficult to determine, but possibly due to the prospective readers having access to the medical record and thus a clinical context than the blinded retrospective readers.

Tc-99 m sestamibi imaging of the gallbladder has some challenges. Most notably, its renal activity could be mistaken as the

gallbladder or decrease confidence in gallbladder visualization due to overlapping viscera on planar imaging. Although SPECT/CT appears to improve the specificity/PPV in challenging cases, and was utilized clinically in 8 of 39 cases (21 %), the analysis did not demonstrate it was statistically significant. Our blinded reviewers requested a desire for SPECT/CT images in 0 %–38 % of the study cohort. This suggested that SPECT/CT is a desired adjunct if Tc-99 m sestamibi is to be used as a replacement for mebrofenin as it can help delineate the anatomy and the nonspecific uptake present in Tc-99 m sestamibi compared to Tc-99 m mebrofenin scans.

It is known that one method of Tc-99 m sestamibi clearance is through the biliary system [6]. There have been several reports of Tc-99 m sestamibi being used in identifying acute cholecystitis, however, most are individual case reports [7–11]. Additionally, Tc-99 m sestamibi has been shown to detect gastroesophageal reflux during cardiac imaging [17]. However, several prospective and retrospective studies have shown the potential of Tc-99 m sestamibi in hepatobillary imaging. Sadeghi et al. demonstrated utility of Tc-99 m sestamibi for biliary imaging in infantile jaundice [6]. A retrospective study by Semaan et al. using Tc-99 m sestamibi for myocardial imaging were reevaluated and demonstrated efficacy for confirming cystic duct patency for patents presenting with chest pain [12]. More importantly, Kakhki et al. demonstrated that Tc-99 m sestamibi could be used for evaluating gallbladder ejection fraction in patients [13,15]. These studies became the main basis for us changing our clinical protocol in face with the Tc-99 m Mebrofenin shortage.

Our study had several limitations including the limited number of patients, with 39 during the study period. Additionally, only 14 patients had histopathology with the remaining outcomes determined by clinical assessment. SPECT/CT usage was based on the primary reader, with the blinded retrospective physician in several instances wanting SPECT/CT that were never obtained. Our control cohort patients (those for parathyroid imaging) imaging with Tc-99 m sestamibi had a modified hepatobiliary scan protocol to make sure imaging didn't interfere with the time points images required for the primary indication and lacked the patient preparation that was normally performed for hepatobiliary scans. Finally, confirming the results of Tc-99 m sestamibi imaging (particularly positive scans for acute cholecystitis) with standard of care mebrofenin only occurred in one case given the shortage.

In conclusion, Tc-99 m sestamibi has excellent sensitivity and negative predictive values for the diagnosis of acute cholecystitis. It can serve as an alternative agent during shortages of standard agents. Future research should include multi-center samples and prospective randomized study designs.

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Data availability statement

All data analysis to support this study was mentioned in the manuscript. Source data can be obtained per request of the contact author.

CRediT authorship contribution statement

Bamidele Otemuyiwa: Writing – original draft. **Matthew S. Davenport:** Writing – review & editing, Formal analysis, Investigation. **Daniel Wale:** Writing – review & editing, Formal analysis, Conceptualization. **Midhhath Afza Munavar Ali:** Writing – review & editing, Investigation. **Benjamin L. Viglianti:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paperThe authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Benjamin Viglianti reports administrative support and article publishing charges were provided by University of Michigan. Benjamin Viglianti reports a relationship with University of Michigan that includes:. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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