Original Article

Role of cholescintigraphy in management of acute acalculous cholecystitis

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ABSTRACT

Aim: This study is aimed to evaluate the role of cholescintigraphy in management of acute acalculous cholecystitis. **Materials and Methods:** A total of thirty two patients who had presented to the surgical out-patient department or referred from in-patient department or intensive care unit between February 2008 and February 2010 were studied. All patients with Ultrasonography abdomen findings of acalculous cholecystitis were included in the study and they underwent cholescintigraphy. Gall bladder ejection fraction (GBEF) was calculated 30 min after fatty meal. Patients who either had non-visualization of gall bladder or GBEF less than 40% were considered to have acalculous cholecystitis on cholescintigraphy. The patients were followed-up for a period of 3 months after the commencement of treatment. **Results:** Eleven patients had either non-visualization of gall bladder or GBEF < 40%. Of these, six patients underwent cholecystectomy and the rest were medically managed, as patients deferred surgery. 83.33% of post-cholecystectomy patients as against 40% of medically treated patients were symptom free. Twenty one patients had GBEF > 40%, 90.74% of these patients were symptom free at the end of 3 months, with medical management. **Conclusion:** Cholescintigraphy is an important adjunct in management of patients with acalculous cholecystitis by guiding the course of therapy-surgical management versus medical management.

Keywords: Acute acalculous cholecystitis, cholescintigraphy, gall bladder ejection fraction

INTRODUCTION

Acute acalculous cholecystitis (AAC) is a well-recognized but still poorly understood entity. It accounts for 5-14% of all cases of acute cholecystitis. It is well-known to occur in very sick patients already admitted in intensive care unit (ICU), e.g., after major trauma, burns, sepsis, major non-biliary surgery and after parenteral feeding, with high incidence of complications such as perforation and high mortality. Compromised perfusion of the metabolically active gall bladder mucosa may also be contributory. Other factors such as prolonged hyperalimentation, prolonged suctioning by nasogastric tube, positive pressure ventilatory support, numerous transfusions, use of vasoactive amines and use of morphine analgesia also have been implicated.[1]

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Most large series have observed that AAC occurs in medically compromised patients. The condition most likely results from a gradual increase in bile viscosity, due to prolonged stasis, that leads to a functional obstruction of the cystic duct. AAC, if not managed effectively, tends to have a more fulminant course, frequently associated with gangrene, perforation, and empyema.[2] Unfortunately, both clinical and laboratory tests lack sensitivity and specificity for arriving at a diagnosis. After AAC is clinically suspected, the next step is to diagnose and evaluate it. The most accessible and portable tool available is the ultrasonography of abdomen.[3] A hepatobiliary iminodiaceticacid (HIDA) scan is advised by the Rome II Consensus Group to be the next step in patient evaluation.[4] The aim of our study was to determine the role of cholescintigraphy in management of patients diagnosed to have acalculous cholecystitis on USG abdomen.

MATERIALS AND METHODS

Patients inclusion criteria

- Patients presenting to the out-patient department (OPD) or referred from in-patient department or ICU during the period between February 2008 and February 2010 were considered.

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- Patients with complaints of flatulent dyspepsia, vomiting, fever, upper abdominal pain and showing possibility of cholecystitis.
- USG abdomen findings suggestive of acalculous cholecystitis This added up to a total of 32 patients.

USG

The criteria for labeling cholecystitis on USG Abdomen were as per previous reports and studies.[3] These were:

- Gall Bladder wall thickness > 4 mm in absence of ascites or hypoalbuminemia.
- Pericholecystic fluid collection.
- Sonographic Murphy's Sign.
- Gall bladder oedema with Sonographic Murphy's Sign and no underlying pathology such as ascites or hypoalbuminemia.

These patients were then subjected to cholescintigraphy.

Cholescintigraphy

Patients were advised nil per orally for 4 hours (h) prior to the study. Patients fasting for more than 12 h were fed with a standardized meal and were on fast for 4-5 h and then taken up for the study. There was a strict adherence to these criteria. This is because a recently ingested meal stimulates endogenous cholecystokinin production, which continues until the food has emptied from the upper small bowel. The rising serum cholecystokinin (CCK) level causes gall bladder contraction, prevents radiotracer entry and may result in a false positive study for acute cholecystitis. On the other hand, fasting for long hours, causes collection of viscous bile and sludge in the gall bladder (GB), thus preventing radiotracer entry and causing false positive results.

Technetium-99m(Tc-99 m) mebrofenin was administered intravenously (A dose of 5 mCi of Tc-99 m mebrofenin was administered in patients with S. Bilirubin < 2 mg/dl and increased up to 10 mCi in patients with S. Bilirubin > 10 mg/dl). The study was performed on Multispect Dual Head Gamma Camera (Siemens, Germany). Low-energy high-resolution parallel hole collimator was used. Serial static isotime** images of the abdomen were acquired in anterior view, at different time intervals with the patient in supine position, up to delayed 4 h images, if the gall bladder was not visualized. In cases where gall bladder was visualized, pre- and post-fatty meal images were also acquired. Right lateral view of the abdomen was acquired when deemed necessary. Fatty meal was formulated as Humana fatty meal formula,[5] 240 ml containing 20 g fats and 415 kcal. Standardization of this fatty meal with GBEF was done based on readings from ten normal volunteers.

(**It was difficult to acquire dynamic 1-1.5 h. images for patients referred from the ICU. Hence, we standardized the protocol to static isotime images).

Image analysis

Studies were analyzed for hepatic uptake and excretion of tracer in to the biliary system, time to visualization of activity in small-bowel, time of visualization of gall bladder. The physiology of gall bladder contraction has been well described.[6,7] Endogenous CCK secreted by the duodenal mucosa in response to fatty meal stimulus peaks during 20-30 min. The CCK levels remain elevated until the meal has passed through the upper small-bowel and promptly return to baseline due to its rapid metabolism (2.5 min serum half-life).[8] Gall bladder contraction is initiated when the serum CCK reaches a threshold that is considerably lower than the peak CCK.[8]Simultaneously, CCK relaxes sphincter of Oddi, allowing bile to empty in to small-bowel.

Hence, in patients where in the gall bladder was visualized, gall bladder ejection fraction (GBEF) 30 min post fatty meal was calculated.

GBEF was calculated by the following formula:

$$\text{GBEF}(\%) = \frac{\text{Net GB count pre fatty meal} - \text{Net GB count post fatty meal}}{\text{Net GB count pre fatty meal}}$$

Scintigraphic criteria for interpretation as acalculous cholecystitis

- Non-visualization of gall bladder
- If gall bladder was visualized, GBEF < 40%

Management criteria

The following patients were taken up for surgery:

- Patients who showed hepatic uptake and excretion of radiopharmaceutical through the common bile duct, however, without visualization of gall bladder until the delayed 4 h image.
- Patient with GBEF < 40%, if they gave an informed consent for surgery.

Patient with GBEF > 40% and those with GBEF < 40% but did not consent for surgery, were taken in to the conservative management arm.

Patients were followed-up in the OPD for 3 months post-commencement of treatment (medical/surgical). They were assessed for the presence of symptoms, and if so, whether there was an improvement or worsening of symptoms.

In addition, post-operative patients were assessed for surgery related symptoms/complications and wound healing.

Statistical analysis

In patients with either non-visualized gallbladder or GBEF < 40%, the odds ratio for the different modes of management was calculated.

RESULTS

I. The findings of cholescintigraphy [Figure 1] were as follows:
   (i) Non-visualization of GB [Figure 2] – 7 (21.87%).
   (ii) GBEF < 40% [Figure 3] – 4 (12.5%).

(iii) GBEF > 40% [Figure 4]– 20 (62.5%).
(iv) Rim Sign – 6 (18.75%).
(v) Duodenogastric reflux – 4 (12.5%).

II. Of the patients suspected to have cholecystitis clinically, 32 patients had USG abdomen findings suggestive of acalculous cholecystitis.
III. Twenty six of the 32 patients had positive sonographic Murphy's Sign. Out of these 26, 10 were having EF < 40% or non-visualization of Gall Bladder.
IV. All patients who had pericholecystic fluid collection were having non-visualization of Gall Bladder on cholescintigraphy. One of these patients had finding of gangrenous gall bladder per operatively [Figure 5].
V. GBEF of < 40% or non-visualization of gall bladder were considered as indicators of better post-operative outcome as suggested by many investigators.
Surgical option was given to patients falling in these two categories. However, as some of these patients denied surgery, they were shifted to control arm and managed conservatively. Of the 11 patients in this category, six underwent cholecystectomy [Figure 6] and 5 were medically managed as per patient's decision. These patients were followed for 3 months and evaluated for symptom relief. Of the surgically treated patients, five were symptomatically better [Table 1]. In the medically treated arm, three out of five patients did not show any improvement in symptoms. Statistically, this does not give a significant '*P*' value. However, 83.33% of the surgically treated group showed improvement as against 40% of the medically treated group [Figure 7,8].
VI. Twenty-one patients had GBEF > 40% and were managed medically and followed-up. Of the medically managed patients, 19 patients improved while two remained the same symptomatically [Table 1]. Of these two patients, one underwent cholecystectomy for persistence of symptoms. Hence, in this group, the percentage of patients having symptomatic improvement was 90.47% [Figure 2].
VII. The odds ratio was found to be 7.4 with a confidence interval of 0.46-122.70.

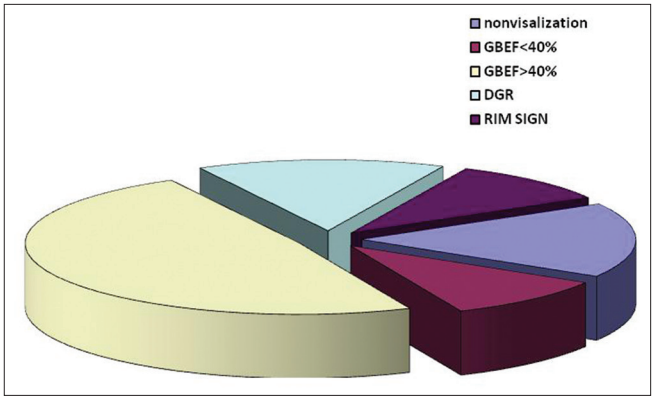

Figure 1: Findings of cholescintigraphy in various patients

DISCUSSION

Imaging Studies have played an incremental role in the diagnosis

Table 1: Comparison of groups according to ejection fraction and management, on follow-up

Group	Better	Same	Total
EF<40% surgical	5 (15.63)	1 (3.12)	6 (18.75)
EF<40% medical	2 (6.25)	3 (9.37)	5 (15.62)
EF>40%	19 (59.37)	2 (6.25)	21 (65.63)
Total	26 (81.25)	6 (18.75)	32 (100)

EF: Ejection fraction

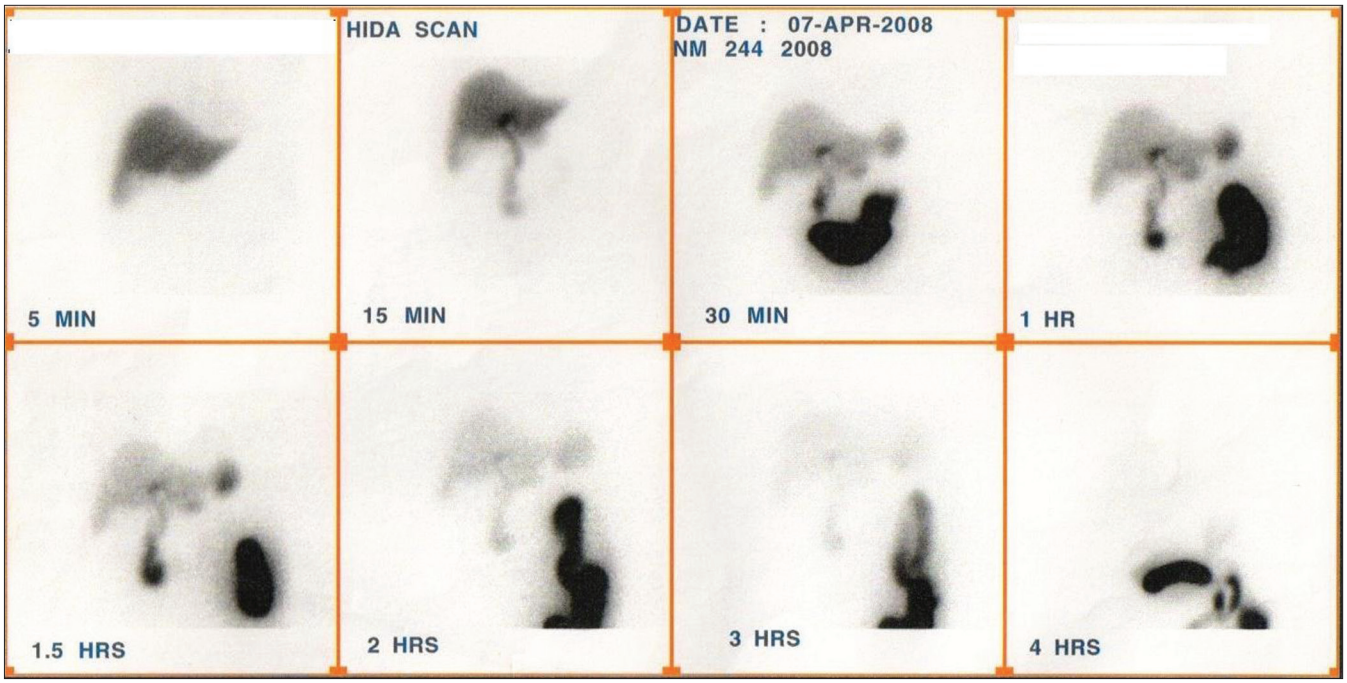

Figure 2: Image of cholescintigraphy in patient with non-visualization of gallbladder

and management of acute cholecystitis. Overall sensitivity and specificity for Hepatobilliary scintigraphy in the diagnosis of acute cholecystitis are 95-100% and 81-100% respectively, whereas the sensitivity and specificity of sonography is reported as 67-93% and 82-100%, respectively.[9-11] These data consist of a majority of cases of acute calculous cholecystitis. The role of imaging studies in establishing the diagnosis and management of AAC is less established.

A 7 years review at Yale University by Savoca *et al*.[12] showed an increasing prevalence of AAC in out-patients with 77% patients developing AAC while at home and 23% while hospitalized. Our study showed 21 patients presenting to out-patients department with AAC which is 65.62%. In-patients consisted 34.38%, out of which 21.88% were in wards and 12.50% in ICU. This data fairly tallies with data provided by Savoca *et al*.[11,12] Some investigators have developed the ultrasonographic scoring system to improve the accuracy in detecting AAC in critically-ill. Two points are given for distention of the gallbladder or thickening of the gallbladder wall, and one point each is given for striated

Figure 3: Image of cholescintigraphy in patient with gall bladder ejection fraction < 40%

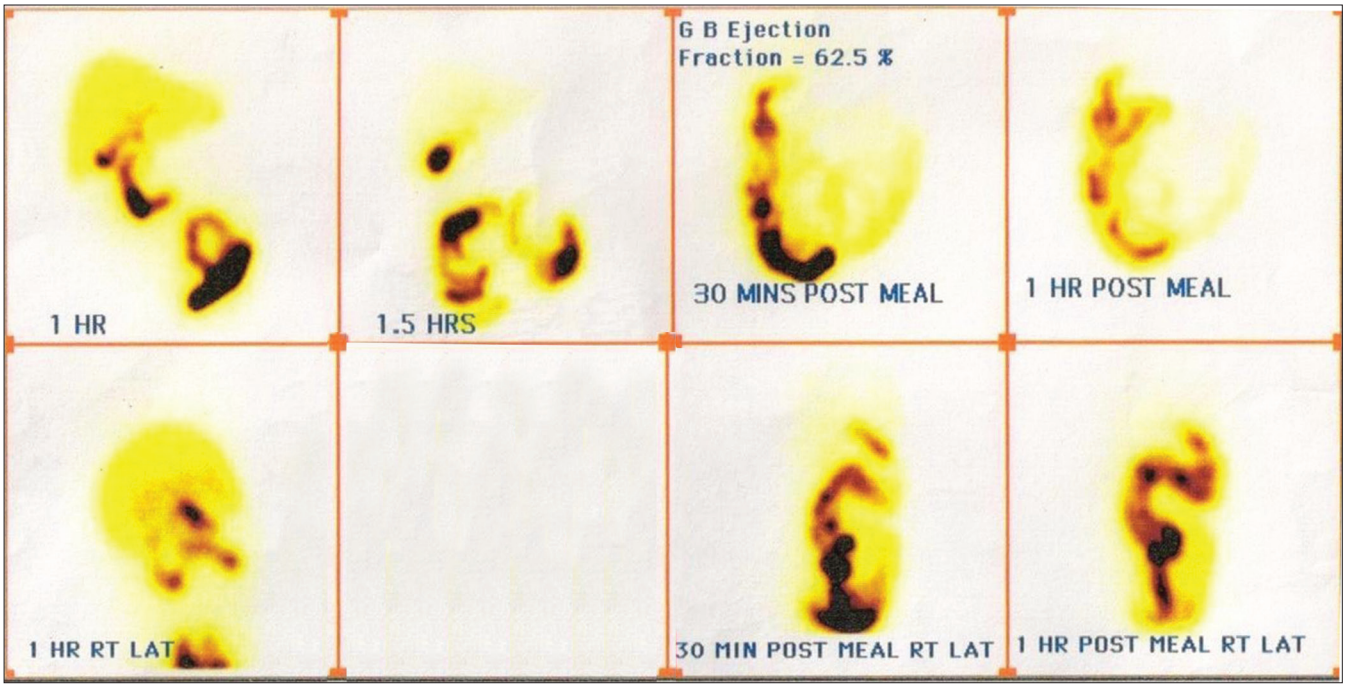

Figure 4: Image of cholescintigraphy in patient with gall bladder ejection fraction > 40%

Figure 5: Gangrenous gall bladder intraoperative photograph in patient with non-visualization of gall bladder on cholescintigraphy

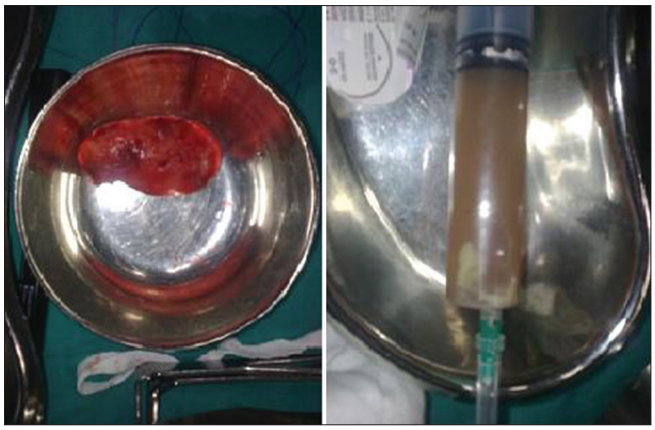

Figure 6: Specimen of empyematous gall bladder in patient with gall bladder ejection fraction < 40% on cholescintigraphy

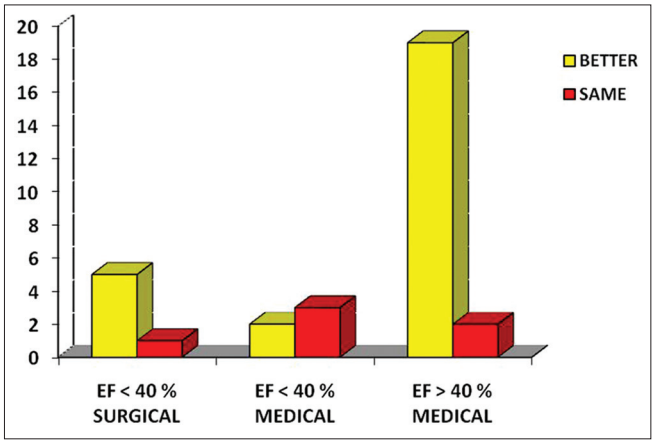

Figure 7: Comparison of various treatment groups according to gall bladder ejection fraction in terms of symptomatic improvement on follow-up

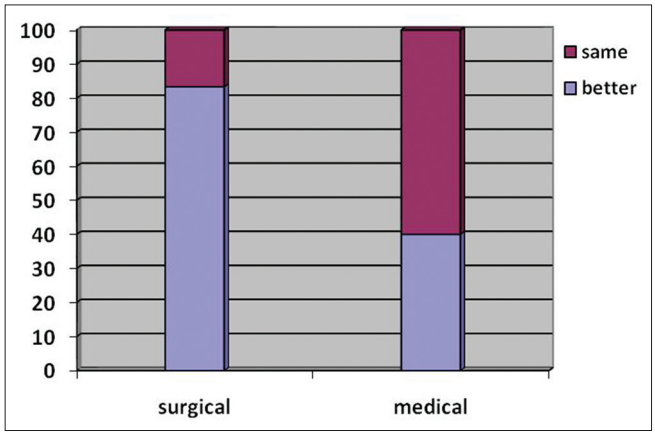

Figure 8: Comparison of treatment groups in patients with gall bladder ejection fraction < 40%

thickening of the gallbladder wall, sludge, or pericholecystic fluid. Scores of six or higher accurately predict acalculous cholecystitis.[3] The overall sensitivity of ultrasonography for detecting AAC has been reported to range from 67% to 92%, with specificity for more than 90%.[13]

A Cholescintigraphy scan has been advised by the ROME II Consensus Group to be the next step in patient evaluation. A Cholescintigraphy Scan can be done using CCK infusion or fatty meal provocation if proper attention to meals and measurement sequence has been given. We used fatty meal provocation method as it is more cost-effective, more physiological and easily available. Proper care was taken to time the sequential scans and the meals. However, a major limitation is the unreliable GBEF values in patients with gastroparesis. These patients have a delayed secretion of endogenous CCK and hence underestimation of GBEF. On the other hand, use of sincalide (synthetic C-terminal octapeptide of CCK) is quicker, reliable and reproducible. It permits better standardization of the procedure.

By the ROME II consensus group[4] criteria, assessment of gall bladder emptying by cholescintigraphy is a decision making tool in the diagnosis of functional gall bladder disorders. They have suggested a limit of GBEF > 40% to call it as normally functioning gallbladder. On the other hand, they also suggested that in presence of normal sonography findings and liver function tests (LFT)/pancreatic enzyme levels and a reduced GBEF, cholecystectomy is recommended. There are three meta-analyses on the issue of predictive value of cholescintigraphy in symptomatic AAC patients. Yap *et al.*[14] studied only symptomatic patients with abnormal and normal cholescintigraphy results who underwent surgery. While study by Ponsky *et al.*[15] and Mahid *et al.*[16] examined outcomes of patients with abnormal cholescintigraphy results who were medically treated compared with those who underwent surgery. These meta-analyses concluded that cholecystectomy is indicated in symptomatic patients with low ejection fraction on cholescintigraphy, however, without gallstones.

Many other authors had tried to address this issue in their work. Our results were comparable to the odds ratio with confidence interval of the work done by Mishkind *et al.*[17][Table 2]. The percentage of patients having symptom relief after cholecystectomy, obtained in our study, is comparable to the results obtained in previous studies [Table 3]. Patients with GBEF > 40% who were managed medically were followed up

Table 2: Comparison of various studies

Author	Surgical	Medical	OR (95% CI)
Misra *et al.*[18]	67/69	12/29	47.46 (9.69-232.44)
Mishknid *et al.*[17]	26/27	12/15	6.50 (0.61-69.14)
Khosla *et al.*[19]	28/30	2/5	21.00 (2.12-208.06)
Middleton *et al.*[20]	134/140	3/41	282.89 (67.1184.42)
Yost *et al.*[21]	26/27	4/6	13.00 (0.95-178.77)
Watson *et al.*[22]	9/9	0/2	95.00 (1.48-6087.66)
Skipper *et al.*[23]	14/17	12/12	0.17 (0.01-3.53)
This study	5/6	3/5	7.4 (0.46-122.70)

OR: Odds ratio, CI: Confidence interval

Table 3: Comparison for symptom relief in various studies

Study	Percentage of symptom relief
Misra *et al.*[18]	97
Khosla *et al.*[19]	94
Present study	83.3
Yost *et al.*[21]	82

after 3 months and revealed a symptom relief rate of 90.47% which is also comparable with previous studies. A small sample size was one of the limitations of the study. A larger number of patients need to be studied in order to draw statistically significant conclusions. Also randomization of patients would have given more reliable results and conclusions.

CONCLUSION

The symptoms of cholecystitis are clearly associated with motility abnormalities of the gall bladder. Cholescintigraphy is a functional study that defines the underlying pathophysiology of the disease and the value of GBEF directly correlates with gall bladder motility. Hence, cholescintigraphy is an important adjunct in management of patients with acalculous cholecystitis. It effectively guides the mode of therapy – surgical management versus medical management.

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