Cracking the silent gallstone code: Wait or operate?

Goswami AG et al. Current insights on asymptomatic gallstones management

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Abstract
The widespread availability of abdominal ultrasound has revealed the common occurrence of asymptomatic gallstones. While the treatment for symptomatic gallstones is clear, the benefits of minimally invasive laparoscopic cholecystectomy have sparked debate about the best approach to managing silent gallstones. The potential for asymptomatic gallstones to become symptomatic or lead to complications complicates the decision-making process regarding surgical intervention, as it's uncertain when or which patients might develop complications. Consequently, risk stratification appears to play a critical role in guiding decisions about silent gallstones. However, there is no definitive evidence to direct management, and a consensus-based on high-quality evidence is yet to be established.

Keywords: Asymptomatic gallstones, Silent gallstones, Cholecystectomy, Gallbladder cancer, Risk stratification

Core Tip: The discussion surrounding silent gallstones remains unresolved. Despite only approximately 20% of gallstones becoming symptomatic, the widespread use of abdominal ultrasounds, coupled with the availability of laparoscopic cholecystectomies and their quick recovery times, promotes the preemptive removal of asymptomatic gallstones. Patients often opt for surgery to avert future complications, including gallbladder cancer in certain areas. The likelihood of
asymptomatic gallstones progressing to symptomatic disease is very low, and complications typically do not arise without symptoms. Given this and the absence of clear guidelines, there is a need for risk stratification to selectively manage those in high-risk groups with silent gallstones.

INTRODUCTION

Gallstone disease, or cholelithiasis, ranks among the most common disorders of the digestive system. Studies estimate that 10 to 15% of adults have gallstones [1]. However, the majority of those with cholelithiasis do not show clinical symptoms, with only about 20% of individuals experiencing biliary symptoms [2]. Patients with asymptomatic gallstones typically follow a benign course, and the likelihood of their condition progressing to symptomatic disease is low. It is uncommon for these patients to develop gallstone-related complications in the absence of any biliary symptoms. Despite this, the frequency of cholecystectomies has seen a 28% increase since 1990, making it one of the most commonly performed abdominal surgeries today [3].

The acknowledged advantages of minimally invasive laparoscopic cholecystectomy compared to traditional open surgery have reignited interest in determining the best approach to managing asymptomatic gallstone disease (AGSD). Additionally, the widespread use of ultrasound as a standard diagnostic tool has revealed the prevalence of silent gallstones, prompting ongoing debate about how to manage them effectively.

WHAT IS AN ASYMPTOMATIC GALLSTONE?

The term "asymptomatic gallstone disease" (AGSD) refers to the presence of gallstones identified during routine abdominal ultrasound examinations without any associated symptoms of gallstone disease, such as a history of biliary pain (pain in the epigastrium or right upper abdominal quadrant that may radiate to the back or right scapula), or complications like acute cholecystitis, cholangitis, or pancreatitis [4]. Determining whether non-specific dyspeptic symptoms, often associated with
gallstones, should guide treatment is challenging. While many of these symptoms may be attributed to irritable bowel syndrome, the presence of silent gallstones introduces uncertainty in deciding if dyspeptic symptoms are a precursor to clear biliary pain. This remains a highly debated issue.

**THE ORIGIN OF THE DEBATE**

The progression of AGSD has been insufficiently studied, with available research lacking robust evidence, primarily because initial studies relied on oral cholecystography (OCG) for diagnosis. OCG, now considered obsolete due to its poor accuracy, has been replaced by abdominal ultrasound (USG)\[6\]. While there are USG-based studies, their small sample sizes limit their applicability \[7, 8\]. Despite these limitations, research indicates that the annual rate of progression from asymptomatic to symptomatic gallstone disease varies between 0.1% and 7.3% \[9-12\]. The transition between asymptomatic and symptomatic states can be subtle, with symptoms ranging from mild to diverse and often nonspecific. A retrospective study found that the rate of symptom development from silent gallstones was higher in the first two years of follow-up and decreased over time. Additionally, studies suggest that 10% of patients develop symptoms within the first five years of follow-up, rising to 20% after 20 years. The likelihood of symptom development also varies by gender, with a lifetime risk of 6.51% for males compared to 22.1% for females \[13\]. The annual incidence of complications in AGSD is estimated to be less than 1.5%. Specifically, about 0.3% of asymptomatic patients might develop acute cholecystitis, 0.2% could experience obstructive jaundice, and less than 1.5% may suffer from acute pancreatitis without any preceding symptoms of pain \[14\]. This uncertainty regarding who will develop serious complications from silent gallstones contributes to the dilemma of how to treat AGSD, especially in the absence of clear guidelines and definitive studies. Patients with silent gallstones are primarily concerned about the possibility of facing significant complications in the future. However, with surgery-related mortality at about 0.1%, this risk is unlikely to be a major factor in the decision-making process for surgical intervention \[15\]. Given the approximately 20% lifetime risk of progressing to symptomatic disease compared to the low morbidity associated with modern laparoscopic surgery, there may be a negative bias against opting for
surgery. Instead, employing a risk stratification system that predicts a higher likelihood of developing symptomatic disease might be a more rational approach to determining when and for whom surgery should be considered.

The intriguing link between gallstones and gallbladder cancer (GBC) deserves mention. Although the duration, size, and number of gallstones correlate with an increased incidence of malignancy in certain high-risk populations, a direct cause-and-effect relationship has not been conclusively proven \[^{16}\]. Observations of progressive changes in the gallbladder mucosa—from metaplasia to dysplasia, to cancer in situ, and finally invasive cancer—in the presence of gallstones, as reported in Chile, lend some support to the possibility of an association. However, the nature of this relationship remains unclear. The connection is likely more complex, given that geographical regions with a high prevalence of gallstones do not necessarily report a high incidence of GBC, and not all cases of GBC are associated with gallstones.

**RISK STRATIFICATION**

Identifying factors that elevate the risk of symptom development, complications, and gallbladder carcinoma in individuals with silent gallstones has been a complex task but essential for discerning those at increased risk of deviating from the natural course of the disease and for predicting the timing of such changes (Table 1) \[^{17-25}\]. This knowledge is crucial for making informed surgical decisions, yet it currently lacks a precise method for calculating individual risk. At this time, it is impossible to predict the likelihood of any given patient developing complications or experiencing symptom onset, as well as the timeline for these events. Nonetheless, risk stratification can play a valuable role in helping patients make informed choices about their treatment options through informed consent.

**THE LIKELY MANAGEMENT STRATEGIES**

For patients with AGSD, treatment options range from non-operative expectant management to cholecystectomy, based on the patient's preference. Before the advent of laparoscopic surgery, open cholecystectomy was the standard treatment. Today,
laparoscopic cholecystectomy is deemed safe, boasting a 0.2% rate of biliary injury and a mere 0.05% mortality rate [26, 27]. Cholecystectomy for these patients might also be performed alongside intra-abdominal surgery for an unrelated condition or prophylactically in specific groups at higher risk of complications. In conclusion, the presence of laparoscopic facilities should not lead to a broadening of the criteria for gallbladder removal [12].

**Expectant management:** The "wait and watch" strategy is the practical approach that recommends treating patients only when symptoms arise [28]. Since the majority of these patients remain asymptomatic, this approach prevents unnecessary treatment. It also eliminates the risks associated with surgery and anesthesia, as well as reducing unnecessary healthcare costs. The disadvantage is the risk that some patients may develop severe complications, such as acute pancreatitis or cholecystitis, during the waiting period. Moreover, emergency surgery, particularly for older patients with comorbidities, may significantly increase the risk of morbidity and mortality. Nonetheless, the rarity of complication development without prior symptoms questions the necessity of prophylactic surgery [29].

**Routine/Prophylactic cholecystectomy:** Laparoscopic cholecystectomy is currently regarded as the gold standard for gallstone disease management, offering significant benefits such as quick recovery, pleasing cosmetic results, low rates of complications, and minimal morbidity, thus providing a definitive solution. It is typically safe, especially when performed without the presence of concurrent abdominal or systemic conditions. However, this practice may lead to overtreatment in a significant portion of the patient population, potentially increasing overall morbidity and mortality rates, in addition to unnecessary costs and demands on the healthcare system.

**Selective Cholecystectomy:** Cholecystectomy, particularly laparoscopic, may be advisable for patients at high risk of developing complications or carcinoma. This includes individuals with chronic hemolytic syndromes, those awaiting solid organ transplantation, and those at increased risk of gallbladder cancer, among others (refer
to Tables 1 and 2). These groups are identified based on research indicating a higher risk of gallstone-related complications, although findings vary \[29\]. Nonetheless, the accurate identification of these high-risk categories requires further investigation.

**Concomitant cholecystectomy:** Research indicates that up to 70% of patients with AGSD undergoing laparotomy for unrelated conditions experience biliary symptoms or complications postoperatively. Approximately 40% of these patients will require a cholecystectomy within a year following the initial surgery \[30-33\]. This evidence suggests that patients with gallstones discovered incidentally might benefit from a cholecystectomy performed "en passant" during another intraabdominal surgery, barring specific contraindications \[33\].

While existing evidence suggests that the risks associated with surgery outweigh the potential complications of leaving silent gallstones untreated, and thus routine/prophylactic cholecystectomy is not recommended, it's important to note that most of these studies are observational and were conducted in the 1990s. Apart from a few exceptions \[15, 18, 19, 34\], many of these studies lack sufficient long-term follow-up. Moreover, there are no randomized trials comparing the long-term outcomes of surgical versus expectant management in patients with AGSD. Additionally, although a direct causal link between gallstones and GBC has not been definitively established, the potential risk cannot be entirely dismissed in populations with a high incidence of GBC, given the disease's poor prognosis and the challenges in early detection. The mere possibility of such a link, even without proven causation, can significantly influence the decision-making process for both patients and surgeons \[35\]. Therefore, it's crucial to acknowledge that future research is needed to provide updated and robust evidence to support informed treatment decisions.

**CONCLUSION**

Patients with AGSD should be fully informed about the natural history of these silent stones, including the available treatment options, along with their benefits, disadvantages, and potential complications and risks associated with surgery, even when laparoscopic. Providing patients with this information will empower them to
make informed decisions regarding their care. The advancements and advantages of laparoscopic cholecystectomy should not automatically lead to its recommendation for the surgical management of these asymptomatic individuals. Current evidence favors "watchful waiting" for most patients, with cholecystectomy being an option only for specific subgroups. There is a need for risk stratification to become more objective, and to better support informed surgical decisions within these select groups. Achieving this will require more comprehensive evidence from larger population studies over longer durations across various ethnic groups, as well as experimental studies designed to compare the long-term outcomes of surgical intervention versus expectant management. Until such evidence is available, the majority of patients with asymptomatic gallstones are best managed without surgery.