## CONTENTS

**EDITORIAL**

- **2686** Antifungal pipeline: Is there light at the end of the tunnel?
  *Schinas G, Spernovasilis N, Akinosoglou K*

- **2692** Cracking the silent gallstone code: Wait or operate?
  *Goswami AG, Basu S*

- **2698** Metabolic dynamics in chronic gastritis: Examining urinary profiles post *Helicobacter pylori* eradication
  *Musharaf I, Nashwan AJ*

- **2701** Pearls of meta-analyses and systematic review in scientific evidence
  *Au SCL*

**MINIREVIEWS**

- **2704** Advanced nanomedicines and immunotherapeutics to treat respiratory diseases especially COVID-19 induced thrombosis
  *Wu J, Zheng Y, Zhang LN, Gu CL, Chen WL, Chang MQ*

**ORIGINAL ARTICLE**

**Retrospective Cohort Study**

- **2713** Clinical efficacy of intradermal type I collagen injections in treating skin photoaging in patients from high-altitude areas
  *Yang B, He A, Bu BB, Zhao G, Zhou QZ, He JH, Liu L, Huang WL, Zhao X*

**Retrospective Study**

- **2722** Multimodal imaging in the diagnosis of bone giant cell tumors: A retrospective study
  *Kou MQ, Xu BQ, Liu HT*

- **2729** Treatment for paraganglioma with stereotactic radiotherapy
  *Pontoriero A, Critelli P, Zeppieri M, Angileri FF, Ius T*

- **2738** Effect of endoscopic full-thickness resection assisted by distal serosal turnover with floss traction for gastric submucosal masses
  *Liu TW, Lin XF, Wen ST, Xu JY, Fu ZL, Qin SM*

- **2745** Relationship between ultrasound parameters of the umbilical and middle cerebral arteries and intrauterine fetal distress
  *Chen J, Liu FX, Tao RX*
Effect of psychological nursing interventions on effectiveness and quality of life in schizophrenia patients receiving modified electroconvulsive therapy

Lu J

Effect of percutaneous electrical stimulation at the Baliao point on preventing postpartum urinary retention after labor analgesia

Wang XQ, Guan LS

Observational Study

Perceptions and factors influencing exercise interventions in elderly patients with debilitating spinal surgery and healthcare professionals: A qualitative study

Cheng RR, Li R

Prospective Study

Helicobacter pylori: High dose amoxicillin does not improve primary or secondary eradication rates in an Irish cohort

Costigan C, O'Sullivan AM, O'Connell J, Sengupta S, Butler T, Molloy S, O'Hara FJ, Ryan B, Breslin N, O'Donnell S, O'Connor A, Smith S, McNamara D

Clinical and Translational Research

Causal relationships between gut microbiota and dementia: A two-sample, bidirectional, Mendelian randomization study


Causal association between 25-hydroxyvitamin D status and cataract development: A two-sample Mendelian randomization study

Wang CH, Xin ZK

SYSTEMATIC REVIEWS

Fat management in upper blepharoplasty: Addition or subtraction blepharoplasties, how and when

Miotti G, Di Filippo J, Grando M, Salati C, Parodi PC, Spadea L, Gagliano C, Musa M, Zeppieri M

META-ANALYSIS

Iron and ferritin effects on intensive care unit mortality: A meta-analysis

Yang DC, Zheng BJ, Li J, Yu Y

CASE REPORT

Secondary diabetes due to different etiologies: Four case reports

Song WR, Xu XH, Li J, Yu J, Li YX

Giant cavernous aneurysms occluded by aneurysmal thrombosis, calcification, parent artery occlusion: A case report and review of literature

Wang MX, Nie QB
<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2831</td>
<td>Computed tomography three-dimensional reconstruction in the diagnosis of bleeding small intestinal polyps: A case report</td>
<td>Zhang SH, Fan MW, Chen Y, Hu YB, Liu CX</td>
</tr>
<tr>
<td>2837</td>
<td>Managing adult-onset Still's disease in pregnancy: A case report</td>
<td>Kang JH</td>
</tr>
<tr>
<td>2847</td>
<td>Conversion therapy of a giant hepatocellular carcinoma with portal vein thrombus and inferior vena cava thrombus: A case report and review of literature</td>
<td>Song WJ, Xu J, Nie Y, Li WM, Li JP, Yang L, Wei MQ, Tao KS</td>
</tr>
<tr>
<td>2856</td>
<td>Migration of varicocele coil leading to ureteral obstruction and hydronephrosis: A case report</td>
<td>Alamri A</td>
</tr>
<tr>
<td>2869</td>
<td>Giant vascular malformations invading the skull: A case report</td>
<td>Xie MC, Wang FX, Xu J</td>
</tr>
<tr>
<td>2876</td>
<td>Uterine epithelioid trophoblastic tumor with the main manifestation of increased human chorionic gonadotropin: A case report</td>
<td>Huang LN, Deng X, Xu J</td>
</tr>
<tr>
<td>2887</td>
<td>Clinicopathological analysis of EWSR1/FUS::NFATC2 rearranged sarcoma in the left forearm: A case report</td>
<td>Hu QL, Zeng C</td>
</tr>
<tr>
<td>2894</td>
<td>Thoracic giant cell tumor after two total en bloc spondylectomies including one emergency surgery: A case report</td>
<td>Liang HF, Xu H, Zhan MN, Xiao J, Li J, Fei QM</td>
</tr>
<tr>
<td>2904</td>
<td>Primary thoracolumbar intraspinal malignant melanoma: A case report</td>
<td>Huang JB, Xue HJ, Zhu BY, Lei Y, Pan L</td>
</tr>
</tbody>
</table>
ABOUT COVER
Peer Reviewer of World Journal of Clinical Cases, Shyam Sundar Das Mohapatra, DNB, MBBS, Surgeon, Department of Comprehensive and Community Ophthalmology, Sri Sankaradeva Nethralaya, Guwahati 781028, Assam, India. drssdasmohapatra@gmail.com

AIMS AND SCOPE
The primary aim of World Journal of Clinical Cases (WJCC, World J Clin Cases) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING
The WJCC is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for WJCC as 1.1; IF without journal self cites: 1.1; 5-year IF: 1.3; Journal Citation Indicator: 0.26; Ranking: 133 among 167 journals in medicine, general and internal; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Si Zhao; Production Department Director: Xue Gao; Cover Editor: Jin-Lai Wang.

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
Bao-Gan Peng, Salim Surani, Jerzy Tadeusz Chudek, George Kontogeorgos, Maurizio Serati

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2307-8960/editorialboard.htm

PUBLICATION DATE
June 6, 2024

COPYRIGHT
© 2024 Baishideng Publishing Group Inc
Cracking the silent gallstone code: Wait or operate?

Aakansha Giri Goswami, Somprakas Basu

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.

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 cholecystectomy 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 "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[5]. OCG, now considered obsolete due to its poor accuracy, has been replaced by abdominal ultrasonography (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[17-21] (Table 1). 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[22-25].

<table>
<thead>
<tr>
<th>Patient-related</th>
<th>Gall stones/gall bladder related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 55 yr</td>
<td>Calculi &gt; 2 cm in diameter</td>
</tr>
<tr>
<td>Female</td>
<td>Three or more gallstones</td>
</tr>
<tr>
<td>Smoking</td>
<td>Floating stones</td>
</tr>
<tr>
<td>High BMI</td>
<td>Calculi &lt; 3 mm with patent cystic duct</td>
</tr>
<tr>
<td>Transplant patients (before or during transplantation)</td>
<td>Non-functioning GB</td>
</tr>
<tr>
<td>Chronic hemolytic conditions (e.g., sickle cell anemia)</td>
<td>GB: Gallbladder; BMI: Body mass index.</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
</tbody>
</table>

**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 GBC, among others[21-25] (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
Table 2 Patients at risk of gallbladder cancer

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallstones associated polyps &gt; 1 cm</td>
</tr>
<tr>
<td>Calcified GB (?)</td>
</tr>
<tr>
<td>Gallstones &gt; 3 cm</td>
</tr>
<tr>
<td>GB packed with stones</td>
</tr>
<tr>
<td>Ethnic groups in high-incidence GBC areas:</td>
</tr>
<tr>
<td>Uttar Pradesh and Bihar in North India</td>
</tr>
<tr>
<td>American Indians</td>
</tr>
<tr>
<td>Mexican Americans</td>
</tr>
<tr>
<td>Residents of Chile, Colombia, and Bolivia</td>
</tr>
</tbody>
</table>

GB: Gallbladder; GBC: Gallbladder cancer.

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[5,18,19,34], many of these studies lack sufficient long-term follow-up. Moreover, there are no randomized trials comparing the long-term outcomes of surgical vs 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 vs expectant management. Until such evidence is available, the majority of patients with asymptomatic gallstones are best managed without surgery.

FOOTNOTES

Author contributions: Basu S conceived the idea; Basu S and Goswami AG collected, analysed, interpreted the data, wrote and prepared the manuscript. All authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest with any individual(s) or any organization.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: China

ORCID number: Somprakas Basu 0000-0003-1903-3438.

REFERENCES


