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Cholecystectomy for asymptomatic gallstones: Markov decision tree analysis

Lee BJH *et al.* Cholecystectomy for asymptomatic gallstones

Brian Juin Hsien Lee, Qai Ven Yap, Jee Keem Low, Yiong Huak Chan, Vishal G Shelat

Abstract

Gallstone is a common public health problem, especially in developed countries. There are an increasing number of patients who are diagnosed with gallstones due to increasing awareness and liberal use of imaging, with 22.6%-80% of gallstone patients being asymptomatic at the time of diagnosis. Despite being asymptomatic, this group of patients are still at life-long risk of developing symptoms and complications such as acute cholangitis and acute biliary pancreatitis. Hence, while early prophylactic cholecystectomy may have some benefits in selected groups of patients, the current standard practice is to recommend cholecystectomy only after symptoms or complications occur. After reviewing the current evidence about the natural course of asymptomatic gallstones, complications of cholecystectomy, quality of life outcomes, and economic outcomes, we recommend that the option of cholecystectomy should be discussed with all asymptomatic gallstone patients. Disclosure of material information is essential for a reasonable patient to make an informed choice for prophylactic cholecystectomy. It is for the patient to decide on watchful waiting or prophylactic cholecystectomy, and not for the medical community to make a blanket policy of watchful waiting for asymptomatic gallstone patients. For patients with high-risk profiles, it is clinically justifiable to advocate cholecystectomy to minimize the likelihood of morbidity due to complications.

Key Words: Asymptomatic; Cholecystectomy; Cholelithiasis; Gallbladder; Gallstone

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Core Tip: We recommend that an option of cholecystectomy should be discussed with all asymptomatic gallstone patients. Disclosure of material information is essential for a reasonable patient to make an informed choice for prophylactic cholecystectomy. It is for the patient to decide on watchful waiting or prophylactic cholecystectomy, and not for the medical community to make a blanket policy of watchful waiting for asymptomatic gallstone patients. For patients with high-risk profiles, it is clinically justifiable to advocate cholecystectomy to minimize the likelihood of morbidity due to complications.

INTRODUCTION

Gallstone, or cholelithiasis, is a common public health problem, especially in developed countries^[1-3]. In the United States alone, an estimated 20-25 million Americans have gallstones, and over 700000 cholecystectomies are performed annually, costing a median of USD 11584 per discharge and USD 6.2-6.5 billion^[2,4-6]. There are three main types of gallstones – cholesterol stones, brown pigment stones, and black pigment stones, with cholesterol stones accounting for 80%-90% of all gallstones^[1]. Many risk factors predispose an individual to develop gallstones, broadly classified into modifiable and non-modifiable factors. Modifiable risk factors include rapid weight loss, diet, drugs such as hormone replacement therapy and fibrates, and metabolic syndromes such as type two diabetes mellitus and non-alcoholic fatty liver disease^[7,8]. Examples of non-modifiable risk factors are female gender, race and hemoglobinopathies like sickle cell disease and spherocytosis^[7-11]. Additionally, chronic *Salmonella typhi* gallbladder infection also predisposes to gallstones.

Ultrasonography (US) is the gold standard for gallstone diagnosis due to its non-invasive nature and high sensitivity and specificity^[12]. Universal accessibility and affordability of US scans have bolstered epidemiological studies on gallstone prevalence. The gallstone burden varies across different populations. For example, Western populations report gallstone prevalence of 0.1%-61.5%^[1,13] compared to 3%-15.6% in the Asian populations^[2,12,14]. Overall, many patients are diagnosed with asymptomatic gallstones due to increasing awareness and liberal use of imaging^[15]. An estimated 22.6%-80% of gallstone patients are asymptomatic at the time of diagnosis^[16-18]. However, asymptomatic gallstone patients are still at life-long risk of developing symptoms and complications. Gallstone diseases are associated with significantly higher all-cause mortality than individuals without gallstones^[19,20]. In addition, gallstone diseases are associated with comorbidities such as cardiovascular diseases like hypertension, hyperlipidemia and malignancies^[21,22]. Thus, early prophylactic cholecystectomy could reduce some risk burden, especially in selected patients. However, the current standard of practice is to recommend cholecystectomy only after symptoms or complications have occurred.

One of the earliest and most common presenting complaints in patients with symptomatic gallstones is biliary colic^[18,23]. Sometimes, biliary colic can be confused with dyspepsia or atypical chest pain, resulting in a delayed diagnosis of gallstone disease. This subsequently increases the risk of complications like acute cholecystitis, acute cholangitis and acute biliary pancreatitis. If timely intervention is not done, severe complications like Mirrizzi's syndrome, cholecystoenteric fistula, pyogenic liver abscess, and gallstone ileus can develop^[24]. Clinical outcomes of patients with complicated gallstone disease are inferior to elective laparoscopic cholecystectomy for symptomatic biliary colic patients^[25,26].

Since 1985, laparoscopic cholecystectomy has replaced traditional open cholecystectomy as the gold standard for managing gallstones and related complications^[27,28]. Therefore, it is intuitive to ask ourselves, can elective laparoscopic cholecystectomy in asymptomatic gallstone patients reduce the overall morbidity and

mortality from gallstone disease? For conclusive logical reasoning, we need to review the current evidence about the natural course of asymptomatic gallstones, complications of cholecystectomy, quality of life outcomes, emerging concerns of gut microbiome alteration following cholecystectomy, and ethical and economic considerations. Furthermore, as bile duct injury (BDI) is an Achilles heel of cholecystectomy, it is integral that we include BDI in our discussion.

THE NATURAL COURSE OF ASYMPTOMATIC AND SYMPTOMATIC GALLSTONE PATIENTS

William Mayo stated, "There is no innocent gallstone". The progression from asymptomatic to symptomatic gallstone disease is variable, ranging from 11.7%-23.7% over 9 to 20 years^[29-32]. The cumulative incidence of developing complications for asymptomatic gallstone patients was about 3%-8% over the same period^[29-31,33]. In contrast, prior population studies have reported that the rate of recurrent symptoms in already symptomatic patients was significantly higher, ranging from 18.6%-37.1% over 1 to 14 years^[13,34-38]. Similarly, this group of patients was also at a higher risk of developing complications, ranging from 4%-30.3% over the same period^[36-38].

Overall, the cumulative incidences of cholecystectomy due to recurrent symptoms or complications was 22.3%-50.7% in symptomatic gallstone patients^[34,36-38], which were substantially greater compared to the 8.3%-25.8% of those who were asymptomatic and eventually underwent cholecystectomy^[29,30,32,33].

PREVAILING PRACTICE FOR MANAGING ASYMPTOMATIC GALLSTONE PATIENTS

The blanket policy for asymptomatic gallstone patients is currently watchful management, except in selected scenarios. Cholecystectomy is not routinely offered due to the inherent risks of surgery. These include risks of anesthesia, potential vascular and bowel injuries, retained stone, bile leak, BDI (estimated incidence of 0.2%-0.8%), and postcholecystectomy syndrome (PCS)^[39,40], which are discussed below.

RISK OF POSTCHOLECYSTECTOMY SYNDROME

PCS encompasses symptoms and signs due to biliary and non-biliary sequelae of surgery^[41,42]. These heterogeneous complexes of symptoms include abdominal pain, dyspepsia, and jaundice. The prevalence of PCS has been reported to range from very low to 47%^[41-44]. In a study by Shirah *et al*^[41] of 272 patients with PCS, recurrent or retained common bile duct (CBD) stone, cystic duct stump syndrome, CBD stricture, bile leakage, and stenosis of the sphincter of Oddi accounted for 34.9% of PCS. Thus, with the increasing number of cholecystectomies, the number of patients suffering from PCS and related morbidity is likely to rise^[45]. Hence, routine cholecystectomy is not recommended for most patients with asymptomatic gallstones^[15]. However, we argue that some of the PCS complications are a result of technical difficulty following a chronic gallbladder pathology, thus early cholecystectomy could at least in part, reduce the PCS morbidity. Furthermore, the term PCS is loosely interpreted in the literature; and patients with obvious diagnoses of bile leak, CBD stone, *etc.* should not be classified as having PCS.

CHANGES IN GUT MICROBIOME

Removal of the gallbladder is associated with two times increased enterohepatic circulation, with increased bile acid exposure of the intestinal mucosa. This physiologic change leads to an altered gut microbiome. The intestinal microbiome is implicated in gallstone diseases and has relevance both as a causative and end effect. Frost *et al*^[46] studied the fecal microbiota profile of 404 gallstone carriers, 580 individuals post-cholecystectomy, and 984 healthy controls using the 16S rRNA gene sequencing technique. The participants were matched for age, sex, body mass index, smoking habits, and food-frequency-score. They did not observe significant differences in microbiota composition of gallstone carriers and controls. However, cholecystectomy patients exhibited reduced microbiota diversity, reduced potentially beneficial genus *Faecalibacterium*, and increased opportunistic pathogen *Escherichia/Shigella*. A decrease of *Faecalibacterium* reduces short-chain fatty acid production. Thus, colonocytes are

deprived of energy, and the colon is subjected to a pro-inflammatory intestinal state. In a meta-analysis including 10 cohort studies and 524649 patients, Zhang *et al*^[47] reported that cholecystectomy patients have an increased risk of colorectal cancer. The opportunistic pathogens may induce DNA damage, increase gene mutagenicity, and increase lipopolysaccharide synthesis. Lipopolysaccharide promotes liver metastases in colorectal cancer patients by stimulating toll-like receptor 4 signalling^[48]. More data is necessary to establish if cholecystectomy increases colorectal cancer risk. If a causal link is established, information disclosure during informed consenting would be material from a reasonable patient perspective.

IMPACT ON QUALITY OF LIFE

Aside from the risks of surgery, multiple studies have documented the decrease in quality of life (QOL) post-cholecystectomy for asymptomatic gallstone patients^[49-51]. Quintana *et al*^[52] also reported a poorer health-related QOL risk to benefit ratio for patients with asymptomatic gallstones post cholecystectomy. For example, in the Short Form 36 (SF-36), patients with symptomatic gallstones and low surgical risks reported an increase in their SF-36 scores and hence improvement in their QoL post-cholecystectomy under the social function (+9.88), bodily pain (+13.76), and mental health (+0.51) domains, respectively. In contrast, patients with asymptomatic gallstones and low surgical risk had minimal improvements in their social function (+0.57) and bodily pain (+2.62) scores post-cholecystectomy while there was a decrease in their mental health scores (-4.16). In another study on prophylactic cholecystectomy for patients with mild hereditary spherocytosis, there was a decrease in quality-adjusted days for patients with asymptomatic gallstones post-cholecystectomy (-46 to -167) compared to patients with biliary colic (-129 to +156)^[10]. However, it is also possible that delays to cholecystectomy increase the likelihood of needing endoscopic retrograde cholangiopancreatography (ERCP) for CBD stone and its relevant clinical manifestations like cholangitis or pancreatitis. It is reported that ERCP reduces the QoL in patients with

choledocholithiasis^[53]. Thus, more evidence is necessary to study the true impact of prophylactic cholecystectomy on QoL of asymptomatic gallstone patients.

ETHICAL IMPLICATIONS OF PROPHYLACTIC SURGERY

Prophylactic cholecystectomy on asymptomatic gallstone patients also has its ethical implications. An example of an ethically justified prophylactic surgery is prophylactic mastectomy, commonly performed for patients at risk of breast cancer. These include patients with BRCA1 mutations, strong family history of breast cancer with no demonstrable mutations, and tumors with histological risk factors such as unilateral ductal carcinoma in situ^[54-57]. This is because female patients with BRCA1 mutations have an 80%-90% lifetime risk of developing breast cancer compared to the 5.7%-12.6% risk in the general population^[58-60]. Similarly, Zendejas *et al*^[61] reported that prophylactic mastectomy, costing \$36594, provided 21.22 mean quality-adjusted life-years (QALY) compared to the 20.93 QALY for surveillance, which cost \$35182. This gave an incremental cost-effectiveness ratio (CER) of \$4869 per QALY gained for prophylactic mastectomy. Therefore, it is ethical and beneficial to perform prophylactic mastectomy in asymptomatic high-risk female patients to reduce the likelihood of developing breast cancer^[62,63].

In contrast, although 85% of gallbladder cancer were associated with the presence of gallstones, the actual incidences of gallbladder cancer were low, ranging from 0.3%-3%, with the highest incidences seen in patients of Indian descent^[64-67]. The 20-year cumulative risk of gallbladder cancer in patients with gallstones was also reported to be low at 0.13%-1.5%^[68]. Additionally, in a study by Wanjura *et al*^[69], while there was QOL improvement, the Gastrointestinal Quality-of-Life Index scores were lower in the patient's post-cholecystectomy (115.2) compared to the background population (116.7). In this aspect, the benefits of prophylactic cholecystectomy for all gallstone patients may not be comparable to those of prophylactic mastectomy. However, prophylactic cholecystectomy for asymptomatic gallstone patients may be considered in countries with a high prevalence of gallbladder cancer^[70,71].

FINANCIAL CONSEQUENCES ON THE HEALTHCARE SYSTEM

Offering prophylactic cholecystectomy for asymptomatic gallstone patients also has financial consequences on the healthcare system. An increasing number of individuals with health insurance coverage may lead to overservicing with strains on healthcare infrastructure and resources. For example, a study done by Ellimoottil *et al*^[72] found that insurance expansion in Massachusetts led to a 9.3% increase in elective surgery. On a similar note, Barros *et al*^[73] reported that private health insurance played a key factor in the overwhelming healthcare expenditure in Brazil. Thus, offering prophylactic cholecystectomy may encourage individuals with full coverage under health insurance to exploit their health benefits. However, when the therapeutic benefits do not justify the costs, this eventually leads to overutilization and wastage of healthcare resources.

Conversely, the financial benefits of performing early cholecystectomy may outweigh that of delayed cholecystectomy in the setting of complications. For example, Tan *et al*^[74] previously described the median total inpatient costs to be lower in patients who underwent early cholecystectomy (€4400) compared to those who had interval cholecystectomy (€5500). Similarly, the median cost of cholecystectomy in subsidized patients with and without complications across different public healthcare institutions in Singapore was \$2447 (\$2128-\$2989) and \$1788 (\$1296-\$2589), respectively. Assuming an 8% complication rate for asymptomatic gallstones, \$1788 as the cost of uncomplicated laparoscopic cholecystectomy, and \$2447 as the cost of complicated laparoscopic cholecystectomy; if we operate 100 patients before complications develop; we could generate cost savings to treat three additional patients ($(\$1788 \times 92 + \$2447 \times 8) - 1788 \times 100 = \5272). This is simplistic and discounts the morbidity of difficult cholecystectomy, risk of retained stone, management of bile leak, and other potential secondary procedures that are warranted in patients who need bail-out cholecystectomy techniques. Additionally, the finance calculations do not account for the loss of wages, the impact of hospitalization leaves on employers, and an increase in the use of hospital resources and infrastructure. While such calculations are beyond the scope of this paper, it would be

too simplistic to argue against a liberal cholecystectomy policy just on the bases of financial impact as a liberal policy may be more cost-effective in the long run. This assumption is not entirely unreasonable; as a liberal cholecystectomy policy can potentially reduce the complications of severe acute cholecystitis, acute biliary pancreatitis, acute cholangitis, Mirrizzi's syndrome, *etc.*; with the potential of reducing needs for healthcare resource use and related cost-savings.

CHOLECYSTECTOMY FOR ASYMPTOMATIC GALLSTONE PATIENTS - TO DO OR NOT TO DO

Routine treatment of asymptomatic gallstones is not recommended in current guidelines, mainly due to reasons of low annual incidence of developing symptoms and complications, as well as the costs and risks of surgery^[75,76]. It is acknowledged that only a minority of asymptomatic gallstone patients will eventually develop symptomatic gallstone disease or related complications, with an incidence of 1%-4% per year^[13,16,77]. Patients who are less than 55 years old or with greater than 20 years of life expectancy, female gender, smoking history, higher body mass index, presence of three or more stones, floating gallstones, gallstone > 2 cm in diameter, gallstone < 3 mm size with patent cystic duct, and non-functioning gallbladder are associated with a higher likelihood of having symptoms^[15,78,79]. It remains unproven if patients who fall within these criteria would benefit from elective prophylactic cholecystectomy. Routine cholecystectomy in all patients with asymptomatic gallstones may result in anecdotal BDI, anesthesia-related morbidity, the increased overall cost of care and burden on healthcare resources. Thus, selective policy for prophylactic cholecystectomy may be justified and could be considered. There are certain health situations where prophylactic cholecystectomy is beneficial, and these are discussed below.

BENEFITS OF PROPHYLACTIC CHOLECYSTECTOMY FOR PATIENTS WITH EXISTING CONDITIONS

Cholecystectomy can be recommended as a prophylactic option in selected asymptomatic patients. For example, patients with red blood cell abnormalities such as sickle cell anemia and hereditary spherocytosis are predisposed to higher risks of cholelithiasis, with prevalences of 30%-70%^[80-84]. Studies have also shown that gallstone complicated the clinical course of sickle cell anemia in 40% of adolescents and 70% of adults^[9]. Rutledge *et al*^[85] described that 75% of sickle cell anemia patients with asymptomatic gallstones eventually turned symptomatic. More recently, Muroi *et al*^[86] reported that postoperative complications related to sickle cell anemia were less frequent for asymptomatic gallstone patients (11.5%) who received prophylactic laparoscopic cholecystectomy compared to symptomatic gallstone patients (25.5%). In addition, the same group of patients had shorter hospital admissions and potentially avoided complications such as acute cholecystitis and cholangitis^[86]. Hence, prophylactic cholecystectomy is recommended for sickle cell anemia or hereditary spherocytosis patients with concurrent asymptomatic gallstones, along with splenectomy^[87-90].

Similarly, cholecystectomy is also recommended in asymptomatic gallstone patients who are organ transplant recipients. Studies have shown that organ transplant patients with gallstones have a higher incidence of developing symptoms and complications than the general population^[91-94]. For example, Graham *et al*^[94] reported that patients who underwent cholecystectomy prior to transplant had a 0% morbidity and mortality and 4% graft loss compared to patients who underwent cholecystectomy post-transplant who had 19% morbidity, 6% mortality, and 25% graft loss. Similarly, Kao *et al*^[95] reported that for heart transplant patients with asymptomatic gallstones, prophylactic cholecystectomy could result in cost savings of USD 17799 per QALY quality-adjusted life-year. Likewise, patients with neuroendocrine tumors on somatostatin analog treatment like octreotide are at risk of as high as 65% of developing gallstones and subsequently associated biliary complications^[96]. Hence prophylactic cholecystectomy can also be recommended for asymptomatic gallstone patients with neuroendocrine tumors on somatostatin analogs or prior to organ transplant^[97,98].

Other possible considerations for cholecystectomy for asymptomatic gallstone patients include gallstones larger than 3 cm, concurrent gallbladder polyps, concomitant cholecystectomy during bariatric surgery, and existing comorbidities such as diabetes^[99-103], albeit some of these indications are controversial^[104].

RISKS OF WAITING FOR ASYMPTOMATIC GALLSTONE PATIENTS TO TURN SYMPTOMATIC

Performing cholecystectomy on gallstone patients when still asymptomatic puts them at a lower overall risk of surgical complications. For example, waiting for patients to turn symptomatic already puts them at higher perioperative risk, including age-dependent risk factors^[105]. Studies have also demonstrated that early cholecystectomy reduces the risk of developing gallbladder and bile duct malignancies in the presence of polyps, large gallstones, and porcelain gallbladders^[106,107].

In terms of mortality rates, Zheng *et al*^[21] found a significantly lower number of all-cause deaths in patients who received cholecystectomy versus those who did not across two large prospective cohorts. For example, the rate of all-cause death for individuals with gallstone disease in the National Healthcare Service between 1980 to 2012 was 1347 per 100000 each year compared to individuals without gallstone disease, which was 739 per 100000 each year^[21]. Similarly, in Health Professionals Follow-Up Study from 1986 to 2012, the all-cause death rate for individuals with gallstone disease was 2917 per 100000 each year against the 1315 per 100000 each year for individuals without gallstone disease^[21].

Waiting for symptoms and complications to arise inevitably leads to higher risks of performing emergency cholecystectomy instead of elective cholecystectomy, associated with higher mortality rates, morbidity, and conversion to open conversion^[108,109]. Steiner *et al*^[110] reported that laparoscopic cholecystectomy led to a 33% relative risk reduction in operative mortality than open cholecystectomy. Similarly, the rate of open conversion was found to be low in asymptomatic patients (1.5%)^[111], compared to that for patients with symptomatic gallstones (5.9%-9.2%) and in acute cholecystitis (7.5%-26%)^[112,113]. In

a study by Amirthalingam *et al*^[114] on 149 patients who underwent emergency cholecystectomy, the rate of open conversion was also found to be 5.2% in moderate (Tokyo grade II) and severe acute cholecystitis (Tokyo grade III) compared to 0% in mild acute cholecystitis (Tokyo grade I). Open conversion involves inherent risks such as incisional hernias and postoperative abdominal adhesions, which carry their own set of complications like abdominal colic or even intestinal obstruction necessitating surgical intervention^[115]. Multiple studies reported higher rates of abdominal adhesions in patients who underwent open cholecystectomy (45.5%-75%) in contrast to laparoscopic cholecystectomy (0-35%)^[116]. Hence, prophylactic cholecystectomy in asymptomatic gallstone patients can potentially avert these complications.

In the setting of fibrosis or severe inflammation, cholecystectomy is more technically challenging and leads to a higher risk of surgical complications^[117,118]. For instance, Törnqvist *et al*^[119] reported that the adjusted risk of BDI was doubled among patients with acute cholecystitis. In patients with moderate acute cholecystitis (Tokyo grade II), the risk of BDI was more than doubled and increased almost eightfold for severe (Tokyo grade III) acute cholecystitis. Other studies have also reported a positive correlation between the severity of acute cholecystitis and morbidity^[120,121]. The increased BDI risk, especially in complicated cholecystitis, can also precipitate non-surgical issues such as detrimental socioeconomic and QOL impacts on patients^[51,122-124]. Given its severe outcomes, iatrogenic BDI may also result in litigations, adversely impacting the surgeon and the healthcare institution.

Furthermore, once complications occur, or if cholecystectomy is deemed unfeasible, surgeons may resort to bail-out techniques such as subtotal cholecystectomy, which is more technically challenging. Subtotal cholecystectomy leads to added complications such as retained stone, bile leak, and the need for secondary bail-out procedures like ERCP^[125]. For example, the risk of bile duct leaks from subtotal cholecystectomy ranged from 0.6%-18%^[126-128]. Similarly, the risk of recurrent stones ranged from 1.1%-4.6%^[125,127,128]. Hence, performing cholecystectomy while asymptomatic may be ideal in avoiding complications.

Based on the above-mentioned inherent risks of waiting, we suggest that those who are asymptomatic but have multiple small gallbladder stones (< 1 cm), solitary large gallstone (> 1 cm), gallbladder sludge occupying > 50% of the gallbladder volume should have discussions for considering prophylactic cholecystectomy^[129]. Given that gallstones do not dissolve or disappear with time^[130], the stone burden in young patients would either be the same or increase with age. This could result in a further increase in gallstone related complications. In the same vein, fit elderly patients with a high stone burden could be considered for prophylactic cholecystectomy to avoid age-related general anaesthetic risks should complications arise as they age further and become frailer. Besides surgery, there is the option of percutaneous cholecystostomy in this group of elderly frail patients with cholecystitis. However, there are problems related to a permanent or semi-permanent cholecystostomy tube such as tube occlusion, dislodgement, skin excoriation at the exit site because of bile leakage, constant change of dressings or base-plate and the ensuing hospital or clinic visits^[121]. In practice, many patients have found it very uncomfortable to have a permanent tube in situ. Some of our elderly patients have even reconsidered the decision to undergo laparoscopic cholecystectomy after medical optimisation, to improve their QoL.

IMPROVEMENT IN SURGICAL PEDAGOGY AND EQUIPMENT

National Institute of Health report in 1993 advised against expanding the indications of cholecystectomy, just because the laparoscopy technology was widely expanding^[131]. The main concern for not routinely offering cholecystectomy to asymptomatic gallstone patients is the inherent risks of surgery, of which the most common and feared complication is BDI. This is frequently attributed to surgical inexperience and poor training^[132-134]. However, these earlier data that reported surgical risks for cholecystectomy are no more valid with widespread training, especially with laparoscopic cholecystectomy. These include the SAGES safe cholecystectomy program and advocating the "Critical View of Safety" approach, which is strategized to minimize

BDI^[135,136]. Further, in difficult cholecystectomy situations, bail-out strategies aid in reducing BDI risk.

Multiple studies have improved cholecystectomy outcomes over the years due to improved training standards and technological advancements^[137]. Newer surgical pedagogy has been incorporating simulation and virtual reality training to enhance training and transfer skills into real-life practice^[138]. Guidelines and recommendations such as indocyanine green dye fluorescent cholangiography and intraoperative cholangiography have also been set up to decrease the risk of operative complications^[39]. Thus, the risks of performing elective cholecystectomy can be minimized dramatically due to the factors above. However, it would not be prudent to argue for universal prophylactic cholecystectomy, as despite refinements in technique and standardization of surgical training, BDI continues to be reported. Injuries continue to be reported even after the learning curve^[139] or despite resorting to bail-out strategies^[128]. In our opinion, most BDI happens due to difficulty from chronically neglected pathology; and it is possible that prophylactic cholecystectomy could reduce BDI risk.

Further, though BDI is considered the main outcome metric, retained bile duct stone and bile leak are increasingly important key performance indicators. These complications also warrant additional interventions like radiology-guided abdominal cavity drainage or ERCP and biliary drainage. Therefore, we can argue that a prophylactic cholecystectomy could also reduce such risks.

IMPROVEMENT IN IMAGING AND DIAGNOSTICS

Imaging technology is getting sophisticated with improved diagnostic and prognostic accuracy. In addition, the integration of artificial intelligence and machine learning algorithms aid pattern recognition and greatly enhance diagnostics by reducing inter-observer variability. Recently, ¹an international multidisciplinary committee comprising expert radiologists, gastroenterologists, gastrointestinal surgeons, surgical oncologists, ¹medical oncologists, and pathologists reported the Gallbladder Reporting and Data System (GB-RADS) ultrasound risk stratification to improve consistency in United States

1 interpretations, reporting, and assessment of the risk of malignancy in gallbladder wall thickening^[140]. 1 The GB-RADS system recommends six categories (GB-RADS 0-5) of 1 gallbladder wall thickening based on gallbladder wall features, including symmetry and extent (focal *vs* circumferential) of involvement, layered appearance, intramural features (including intramural cysts and echogenic foci), and interface with the liver, with increased probability of malignancy. However, the utility of clinical application of the GB-RADS system for justifying prophylactic cholecystectomy in asymptomatic patients remains to be validated.

MARKOV DECISION TREE ANALYSIS

Markov decision tree analysis was performed to quantify the benefits of cholecystectomy for asymptomatic gallstone patients. The following postulations were made. 40% of asymptomatic gallstone patients will become symptomatic during the life span: With risks of uncomplicated biliary colic (75%), sepsis complications (20%) and acute biliary pancreatitis (5%). Half of the uncomplicated biliary colic patients would proceed with uncomplicated elective laparoscopic cholecystectomy, and the other half will wait for complications before agreeing to cholecystectomy. Amongst the patients with sepsis complications, 85% as having acute cholecystitis and 15% as having acute cholangitis. The severity stratification for acute cholecystitis, acute cholangitis, and acute biliary pancreatitis was applied as per our previous reports^[114,141,142]. Finally, the risk of routine laparoscopic cholecystectomy was assumed as 0.5%, risks of ERCP followed by laparoscopic cholecystectomy at 3%, risks of multiple ERCPs with laparoscopic sub-total cholecystectomy at 15%-25%, and one-third of patients with percutaneous cholecystostomy would not proceed with cholecystectomy (Figure 1). Using the Markov decision tree analysis, the recovery was estimated to be as low as 75% if we wait for gallstones to become symptomatic. Considering a 0.5% risk of elective cholecystectomy, a recovery probability for a universal cholecystectomy policy improves to 99.5%. This translates to an absolute risk reduction of 24.5% (0.995 minus 0.750) with a number needed to treat (NNT) as about 4. Thus, at the same threshold, four asymptomatic

gallstone patients can be treated as compared to the current policy of treating one patient. To note, this does not account for healthcare resources, cost-effectiveness, personal risk appetites, and local outcomes of gallstone patients.

CONCLUSION

In conclusion, we recommend that an option of cholecystectomy should be discussed with all asymptomatic gallstone patients. Our justifications for this stance address the main considerations of the current guidelines such as the low annual incidence of developing symptoms and complications, as well as the costs and risks of surgery. Disclosure of material information is essential for a reasonable patient to make an informed choice for prophylactic cholecystectomy. Ultimately, patients have the autonomy to choose their preferred intervention, although it may not be the best therapeutic decision in the eyes of the medical community or based on scientific evidence and numbers. The medical community should not make a blanket policy of watchful waiting for asymptomatic gallstone patients. For patients with high-risk profiles, it is clinically justifiable to advocate cholecystectomy to minimize the likelihood of morbidity due to complications.

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