

Review Article

Asymptomatic Cholecystitis Presents a New Challenge for Correcting Treatment Tactics in Patients with Gallstone Disease Rather Than Being an Unsolvable Problem of Biliary Surgery

Syedmohammadamin Hosseini^{1,*} , Arya Asadizeidabadi¹ , Evgeny Tarabrin² , Sergey Muraviev² , Denis Orlushin² 

¹International Surgical Research Association (ISRA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

²Department of Faculty Surgery №2, I. M. Sechenov First Moscow State Medical University, Moscow, Russia

Abstract

Gallbladder stones, or cholelithiasis, represent a significant public health concern, particularly in Russia, with an incidence of 5-6 per 1,000 people annually. Western countries report a prevalence of 10%-20%, which has nearly tripled in the last three decades due to advancements in diagnostic techniques. Notably, the condition disproportionately affects women and the elderly, with a marked increase in prevalence after the age of 70. Approximately 80% of cases are asymptomatic, and the clinical manifestations develop in only 1-4% of patients annually. Despite the rising identification of asymptomatic cases through enhanced imaging, management strategies remain unclear, leading to hesitancy among surgeons regarding surgical intervention. Current guidelines from various national and international bodies, including NICE and ESGE, advocate for a watch-and-wait approach for asymptomatic patients, citing spontaneous stone clearance. However, the treatment of asymptomatic choledocholithiasis remains contentious, with some guidelines supporting intervention. This ambiguity is compounded by the recognition that complications can arise from unnecessary cholecystectomy, with 10-40% of patients experiencing ongoing symptoms post-surgery. The article emphasizes the need for a comprehensive understanding of asymptomatic cholecystitis, advocating for a meticulous diagnostic approach that considers the potential underlying causes of gallstone formation. The lack of consensus in current literature regarding management strategies highlights the necessity for further research into the natural history of asymptomatic gallstones and the implications of various treatment options. By addressing these complexities, clinicians can enhance patient outcomes and reduce the incidence of post-cholecystectomy syndrome, ultimately leading to more individualized and effective management strategies for patients with asymptomatic cholecystitis.

Keywords

Asymptomatic Cholecystitis, Clinical Guidelines, Postcholecystectomy Syndrome, Cholecystectomy, Endoscopic Retrograde Cholangiopancreatography

*Corresponding author: m.aminhosseini2000@gmail.com (Syedmohammadamin Hosseini)

Received: 24 July 2024; **Accepted:** 20 August 2024; **Published:** 30 August 2024



Copyright: © The Author(s), 2024. Published by Science Publishing Group. This is an **Open Access** article, distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

1. Introduction

Gallbladder stones are a common public health problem, especially in Russia, where the annual incidence of cholelithiasis averages 5-6 people per 1000 population. In Western nations, gallbladder stones affect 10%-20% of the population, with the incidence rate nearly tripling over the past 30 years, largely due to improved diagnostics. It has been determined that the disease is more common in certain age and sex groups. Distinct gender and age disparities in disease prevalence have been identified. Women are five to six times more likely than men to develop cholelithiasis. The prevalence of this condition markedly rises with age, reaching 30% or more after 70 years, meaning the pathology has become one of the serious geriatric problems [1]. The prevalence of asymptomatic calculous cholecystitis is higher than that documented in the literature. Approximately 80% of cholelithiasis cases are asymptomatic. It is reasonable to infer that most of the time the disease will remain asymptomatic throughout an individual's life based on the analysis of the disease's course. Clinical manifestations develop in 1-4% of patients annually, with symptoms manifesting in 20% of patients within 20 years of diagnosis [2, 3, 15]. With the increased emphasis on medical screening and the advancements diagnostic imaging techniques such as magnetic resonance imaging, endoscopic retrograde cholangiopancreatography, and endoscopic ultrasound, an increasing number of asymptomatic cases of cholelithiasis are being identified.

However, asymptomatic cholecystitis is frequently downplayed or disregarded. Surgeons often refrain from investigating this pathology due to the lack of a standardized approach to treatment. Many surgeons are hesitant to decide on surgical treatment, and a smaller part chooses cholecystectomy without clear indications for it. Consequently, most cases of post-cholecystectomy syndrome are precisely in patients operated on for asymptomatic cholecystitis.

2. Method

The management course for these patients remains unclear in clinical recommendations. On one hand, it is stated that a meticulous approach is necessary when examining these patients. On the other hand, the conclusion of the recommenda-

tions emphasizes that research on the management of patients with asymptomatic cholecystitis is a priority within the scientific community focused on cholelithiasis. There is little debate among clinicians regarding the treatment of symptomatic choledocholithiasis, which can lead to life-threatening conditions. However, the treatment of asymptomatic choledocholithiasis is becoming increasingly controversial. Every treatment option carries a certain risk of adverse events, and endoscopic retrograde cholangiopancreatography is no exception.

Eight relevant reports and four national guidelines have been published by the National Institute for Health and Care Excellence (NICE) in the UK, the European Society for Gastrointestinal Endoscopy (ESGE), the British Society of Gastroenterology (BSG), and the European Association for the Study of the Liver (EASL) on the management of asymptomatic choledocholithiasis [14]. Further information is available in Table 1. Among them, three have shown the expediency of a watch and wait strategy due to spontaneous stone clearance. Thus, according to EASL guidelines, treatment of patients with asymptomatic gallstones is not recommended (weak recommendation based on very low-quality evidence) [6]. Some patients may experience persistent or recurrent symptoms after cholecystectomy. Indeed, 10-40% of patients report ongoing complaints following cholecystectomy, sometimes occurring after a short asymptomatic period [7]. Meanwhile, three out of the four national guidelines (NICE, ESGE and BSG) support the removal of stones from the asymptomatic common bile duct using some form of procedure, although there is little data on the natural course of asymptomatic choledocholithiasis and absence of randomized controlled trials comparing intervention versus observation. As a result, we are now faced with a dilemma.

However, it is undeniable that each study prioritizes the analysis of the cost-effectiveness of laparoscopic cholecystectomy, taking into consideration the clinical progression of the disease in patients with asymptomatic or minimally symptomatic gallstones. Moreover, investigations are conducted on the risk of complications and biliary colic in individuals with bile sludge in the gallbladder or asymptomatic stones in the biliary tract.

Table 1. National guidelines.

Institute	Recommendation
National Institute for Health and Care Excellence (NICE) guidelines 2014	We offer bile duct cleansing and cholecystectomy for people with symptomatic CBD stones.
European Society of Gastrointestinal Endoscopy (ESGE) 2019	Recommends offering stone removal to all patients with CBD stones, with or without symptoms, who are eligible for the procedure. Strong recommendation, evidence Low quality.
British Society of Gastroenterology (BSG)	In line with NICE guidelines, stone removal should be offered to all patients with CBD

Institute	Recommendation
2017	stones. It should be noted that there are no controlled studies examining the natural history of asymptomatic CBD stones. Further research in this area is recommended.
European Association for the Study of the Liver (EASL) 2016	Symptomatic choledocholithiasis should be treated. There are no clear recommendations for the treatment of asymptomatic choledocholithiasis.

3. Result

Therefore, when considering the course of asymptomatic cholecystitis, there is never a clear clinical picture. All that doctors rely on two facts: recurring pain in the right subcostal region and the presence of concretions in the gallbladder. The latter are often discovered during routine abdominal screening examinations. The patient's doubts about the need for surgery are shattered by the argument about the possible complications of long-term stone retention. Moreover, difficulties in interpretation arise when the usual manifestation of common bile duct stones is the same acute biliary colic due to its distension due to partial or complete obstruction as cholelithiasis. This pain is extremely difficult to distinguish from gallbladder stone pain. Unlike gallstones, common bile duct stones are asymptomatic only in 5-12% of cases. Small stones obturating Oddi's sphincter can also cause distal obstruction and acute pancreatitis [10].

However, even when endoscopists fully inform patients about the risks before the procedure, the occurrence of complications after endoscopic retrograde cholangiopancreatography places a physical, psychological, and social burden on patients. In addition, endoscopic retrograde cholangiopancreatography in asymptomatic patients with stones is associated with a higher risk of general and severe complications compared to symptomatic patients with stones.

According to statistical data from various studies, the overall complication rate in the asymptomatic group was higher than that in the symptomatic group (26.4% vs. 11.7%, $P < 0.01$) [13]. Additionally, a higher rate of severe complications is observed in the asymptomatic group compared to the symptomatic group (asymptomatic group: [16.1%] vs. symptomatic group: [3.7%], $P = 0.036$) [12].

This question is the most challenging and contentious in resolving the controversy about necessity of cholecystectomy in patients with asymptomatic cholecystitis. Because the presence of abdominal organ pathology often coexists with asymptomatic cholecystitis, mimicking exacerbation symptoms or organ dysfunction may occur due to the progression of cholelithiasis, leading to morphological changes in the intestine, pancreas, or stomach. Cholecystectomy is not recommended for patients with asymptomatic gallstones and gallbladder polyps ≤ 5 mm in size (strong recommendation based on medium-quality evidence) [6].

During a 15-year observation period, the asymptomatic

course of intrahepatic bile duct stones progressed to clinical symptoms in only 11.5% of patients on average, within 3.4 years. The most common symptoms were colic, jaundice, and fever due to cholangitis [11]. The concept of watchful waiting therapy is also debatable, where according to statistical data, the overall frequency of complications from the biliary tract is recorded less frequently, comprising 6.1% after 1 year, 11% after 3 years, and 17% after 5 years. Asymptomatic disappearance of stones was observed in 19% of patients. When side effects associated with the early endoscopic removal of stones in the asymptomatic group were observed in 32% of patients, including 5.2% with severe pancreatitis [14].

4. Discussion

However, very few researchers and practical doctors consider or choose to address this issue before surgical intervention, instead delving into it only after gallbladder removal, when the patient's existing complaints from asymptomatic cholecystitis persist in the postoperative period. The persistence of symptoms after cholecystectomy is concerning because even after successful surgery, patients need to be examined for the cause of their symptoms. This is a stressful condition, even for those who believe that laparoscopic cholecystectomy is the best method for the treatment of cholelithiasis. Recent studies in the literature have not explored preoperative dyspepsia as a predictor factor of post-cholecystectomy syndrome (PCS). This finding could contribute to the understanding of the pathophysiology of PCS [24]. The causes of dyspepsia are varied, including change in gastric motility, visceral hypersensitivity, *H. pylori* infection, and psychological factors. The absence of the gallbladder after surgery results in a continuous flow of hepatic bile into the duodenum, leading to a rapid enterohepatic bile cycle and excessive bile flow juice into the duodenum. This causes increased duodenal-gastric reflux and results in Oddi sphincter insufficiency, further altered gastric motility. This could explain why patients who had preoperative dyspepsia due to various pathologies may develop new dyspeptic symptoms after surgery, unrelated to cholelithiasis.

Studies on asymptomatic cholecystitis are not only limited but also scattered. At the same time, there is no consensus in both domestic and foreign literature. There is broad agreement among clinicians that patients with symptoms or complications caused by common bile duct (CBD) stones should be offered treatment for cleansing. This is strongly recom-

mended by the best-known national guidelines [4, 5]. This consensus turns into debate and disagreement regarding hidden CBD stones, which may be discovered during cholecystectomy with intraoperative ultrasonography (IOU) or intraoperative cholangiography (IOC), or detected on abdominal imaging performed for other reasons. Although some national guidelines recommend ductal cleansing in asymptomatic patients if they are suitable for the procedure, the evidence is of low quality, and there is still no consensus on the management of these patients. Furthermore, these guidelines also indicate that further research on the natural history of gallbladder stone formation is required. Surgeons and gastroenterologists who manage these patients often face a critical question: do the benefits of performing endoscopic retrograde cholangiopancreatography and ductal cleansing outweigh the procedure's associated risks? Data on the natural history of asymptomatic CBD stones are insufficient. To answer this question, we need to understand the natural history of asymptomatic CBD stones and consequences of leaving them untreated, as well as the benefits and risks of endoscopic retrograde cholangiopancreatography in these patients.

Several studies have focused on pancreatic pathology. The authors frequently attribute the primary cause of glandular pathology cholelithiasis to the symptoms of chronic pancreatitis. However, they overlook the fact that pancreatic insufficiency itself can disrupt lipid metabolism in the body, leading to an increase in bile lipids. There is still no consensus on the association between blood and bile lipids in patients with cholelithiasis: some studies indicate hyperlipidemia in these patients, while others refute this association [24]. Many studies, including epidemiologic ones, have demonstrated an inverse relationship between the concentration of cholesterol and bile acids in blood serum and bile among patients with cholelithiasis. It is believed that serum lipids measured at an arbitrary moment cannot correspond to the true concentration of serum lipids at the critical time of gallstone formation [25]. Consequently, the contradictory literature data regarding the causal link between lipid parameters and cholelithiasis are understandable, which confirms the need for further research in this area.

Many people completely overlook the significance of chronic colitis and its impact on bile recirculation process, the composition of portal blood, and venous return to the liver. The chronic inflammatory reaction not only alters the function of the liver's reticuloendothelial system but also the biochemical composition of bile, causing and maintaining subacute inflammation in the biliary tract and gallbladder. There are few studies on gut microbiota changes in gallstone patients, particularly those with asymptomatic gallstones, and these studies have limitations. For example, they often fail to consider the influence of metabolic factors on gut microbiota. In a study [18] comparing gut microbiota between two groups, one with asymptomatic cholelithiasis and one control group, the abundance of gut microbiota significantly increased in

cholelithiasis patients, whereas the diversity of microbiota decreased compared with healthy controls. The intestinal microbiota represents an important environmental factor contributing to metabolic diseases such as obesity, diabetes, dyslipidemia [25], and hypertension [19], all closely linked to gallbladder stone formation, suggesting that the intestinal microbiota is probably related to gallstones [20]. Abnormal cholesterol and bile acid metabolism and secretion are believed to be primary pathophysiological defects in gallstone formation, with gut microbiota regulating bile acid metabolism by altering the size and composition of the bile acid pool [16]. Gut microbiota also plays a role in many biliary diseases, such as primary biliary cholangitis/cirrhosis and primary sclerosing cholangitis [17]. In another significant study, the gut microbiota at different levels was shown to be altered in gallbladder stone formation, indicating that dysbiosis of the gut microbiota plays an important role in promoting gallbladder stone formation [21, 23]. Intestinal bacteria dissociate bound bile acid into free bile acid via bile salt hydrolase (BSH) and further metabolize free bile acids into secondary bile acids via 7α -dehydroxylation. Currently, only certain intestinal bacteria, including genus *Clostridium* and some strains of *Lachnospiraceae* and *Peptostreptococcaceae*, possess 7α -dehydroxylation activity, known as 7α -dehydroxylating bacteria. These bacteria exhibit bile acid-inducible activity. The abundance and diversity of 7α -dehydroxylating bacteria in the intestinal tract of patients with gallstone disease is poorly understood, and these bacteria constitute a small fraction (< 1%) of the total gut microbiota. However, the impact of these small intestinal microbiota on the host can be enormous, and they can increase the levels of secondary bile acids in the intestinal tract, such as deoxycholic acid (DCA) and lithocholic acid (LCA). These secondary bile acids are returned to the liver via enterohepatic circulation. Since the human liver does not perform 7α -hydroxylation on secondary bile acids, they can accumulate in bile to very high levels [22]. The formation of secondary bile acids by gut microbes holds significant biomedical importance. 7α -dehydroxylating bacteria convert primary bile acids to secondary bile acids, inhibiting the growth of *Clostridium difficile* in the body. Monocytes/macrophages, dendritic cells, and natural killer T cells express the functional bile acid receptor FXR. The study revealed an increase in free and secondary bile acids in the enterohepatic circulation, which may lead to the inhibition of functional FXR in immune cells, promoting the release of inflammatory cytokines that cause local inflammation.

The pathology of the duodenum represents the most characteristic misdiagnosis in the indication for cholecystectomy. Pain in the epigastrium and right subcostal region closely resembles biliary colic. However, for some reason, surgeons lack options for additional examination of all duodenal compartments in patients with asymptomatic cholecystitis or are limited to inspecting the ampulla and duodenum. Simultaneously, inflammation in the duodenum, often associated

with pyloroduodenal transition dyskinesia, and resulting duodenostasis lead to increased pressure within the lumen of the duodenum. Bile flow from the choledochus primarily occurs due to suction by the [duodenum] or under the influence of intraductal pressure. The resulting duodenostasis causes hypertension within the duodenal lumen, thereby impeding bile release, particularly when it thickens. This accounts for the sudden onset of right subcostal pain. However, what relevance does vesicoureteral colic hold in asymptomatic cholecystitis? This remains a question for most surgeons today. In one randomized controlled trial (RCT), 118 patients with post-cholecystectomy pain underwent initial examination [8]. Crystals in duodenal bile were discovered in 12 patients upon microscopy. Following ursodeoxycholic acid administration for several months, abdominal pain typical of biliary system disorders significantly decreased or disappeared. These findings affirm that microlithiasis might underlie post-cholecystectomy pain. Alternatively, could it have been the initial cause of the pain syndrome, as perceived by clinicians as biliary colic? Therefore, performing cholecystectomy seems logical when additional diagnostics to confirm microlithiasis (utilizing microscopy of duodenal or hepatic bile obtained during endoscopic retrograde cholangiopancreatography) could preclude surgical intervention [9]. Considering the relatively nonspecific symptoms of cholelithiasis, other underlying conditions such as functional dyspepsia, irritable bowel syndrome, (duodeno)-gastroesophageal reflux, and sphincter of Oddi dysfunction seem to be more causes of complaints.

Another pathology-confounding to surgeons is renal dysmorphia due to prolonged glomerulonephritis or pyelitis. There is some evidence that renal pathology may be a cause of post-cholecystectomy syndrome. Apparently, this question remains in the shadow of surgical community views.

5. Conclusions

In the first installment of a series focusing on management strategies for patients with asymptomatic cholecystitis, it becomes evident that while the condition exists, efforts to characterize it remain lacking. Current surgical practices often rely on preoperative algorithms, overlooking the underlying causes of stone formation, which are often secondary to other pathological processes. Additionally, the routine performance of cholecystectomy for asymptomatic cases may obscure the true cause of the condition and exacerbate patient concerns. Failure to investigate the etiology of stone formation and asymptomatic cholecystitis can lead to tactical errors and perpetuate the risk of postcholecystectomy syndrome.

Moving forward, there is a need to meticulously examine each stage of the diagnostic process for patients with asymptomatic cholecystitis. This approach will pave the way for a new strategy in biliary surgery, one that prioritizes understanding the underlying causes of the condition and tailoring

management strategies accordingly. By addressing these challenges, clinicians can better optimize patient care and outcomes in the management of asymptomatic cholecystitis.

Abbreviations

CBD	Common Bile Duct
NICE	National Institute for Health and Care Excellence
ESGE	European Society for Gastrointestinal Endoscopy
BSG	British Society of Gastroenterology
EASL	European Association for the Study of the Liver
PCS	Post-Cholecystectomy Syndrome
IOU	Intraoperative Ultrasonography
IOC	Intraoperative Cholangiography
BSH	bile Salt Hydrolase
DCA	Deoxycholic Acid
LCA	Lithocholic Acid
RCT	Randomized Controlled Trial

Acknowledgments

I express my gratitude to Dr. Anna Polunina for her advice and management. Knowledge of the surgical domain was extremely helpful in guiding the course of our study and improving our technique. Their astute recommendations and kind criticism was extremely helpful in improving the overall quality of our work.

CRedit Authorship Confirmation

In the study, Seyedmohammadamin Hosseini was responsible for writing, reviewing, and editing the content, as well as conducting investigations and curating data. Arya Asadizeidabadi contributed to writing, reviewing, and editing, and conducted investigations. Evgeny Tarabrin contributed to supervision, visualization, and review & editing. Sergey Muravev contributed to supervision, visualization, original draft writing, and review & editing. Denis Orlushin contributed to original draft writing and review & editing.

Compliance with Ethical Standards

Disclosure Seyedmohammadamin Hosseini, Arya Asadizeidabadi, Evgeny Tarabrin, Sergey Muraviev, and Denis Orlushin have declared that they have no competing interests.

Author Contributions

Seyedmohammadamin Hosseini: Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Resources, Software, Supervision, Validation
Arya Asadizeidabadi: Funding acquisition, Methodology,

Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] Podoluzhnyi V. I., Complications of gallstone disease, *Fundamental and clinical medicine*. 2011 Volume 2 No. 1 p. 102-114.
- [2] Gracie WA, Ransohoff DF. The natural history of silent gallstones: the innocent gallstone is not a myth. *N Engl J Med*. 1982; 307(13): 798-800. <https://doi.org/10.1056/NEJM198209233071305>
- [3] Friedman GD, Raviola CA, Fireman B. Prognosis of gallstones with mild or no symptoms: 25 years of follow-up in a health maintenance organization. *J Clin Epidemiol*. 1989; 42(2): 127-136. [https://doi.org/10.1016/0895-4356\(89\)90086-3](https://doi.org/10.1016/0895-4356(89)90086-3)
- [4] Gallstone Disease: Diagnosis and Management of Cholelithiasis, Cholecystitis and Choledocholithiasis. London: National Institute for Health and Care Excellence (NICE); October 2014.
- [5] Manes G, Paspatis G, Aabakken L, et al. Endoscopic management of common bile duct stones: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy*. 2019; 51(5): 472-491. <https://doi.org/10.1055/a-0862-0346>
- [6] European Association for the Study of the Liver (EASL). Electronic address: easloffice@easloffice.eu. EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones. *J Hepatol*. 2016; 65(1): 146-181. <https://doi.org/10.1016/j.jhep.2016.03.005>
- [7] Borly L, Anderson IB, Bardram L, et al. Preoperative prediction model of outcome after cholecystectomy for symptomatic gallstones. *Scand J Gastroenterol*. 1999; 34(11): 1144-1152. <https://doi.org/10.1080/003655299750024968>
- [8] Okoro N, Patel A, Goldstein M, Narahari N, Cai Q. Ursodeoxycholic acid treatment for patients with postcholecystectomy pain and bile microlithiasis. *Gastrointest Endosc*. 2008; 68(1): 69-74. <https://doi.org/10.1016/j.gie.2007.09.046>
- [9] Abey Suriya V, Deen KI, Navarathne NM. Biliary microlithiasis, sludge, crystals, microcrystallization, and usefulness of assessment of nucleation time. *Hepatobiliary Pancreat Dis Int*. 2010; 9(3): 248-253.
- [10] Frossard JL, Hadengue A, Amouyal G, et al. Choledocholithiasis: a prospective study of spontaneous common bile duct stone migration. *Gastrointest Endosc*. 2000; 51(2): 175-179. [https://doi.org/10.1016/s0016-5107\(00\)70414-7](https://doi.org/10.1016/s0016-5107(00)70414-7)
- [11] Kusano T, Isa T, Ohtsubo M, Yasaka T, Furukawa M. Natural progression of untreated hepatolithiasis that shows no clinical signs at its initial presentation. *J Clin Gastroenterol*. 2001; 33(2): 114-117. <https://doi.org/10.1097/00004836-200108000-00004>
- [12] Saito H, Kadono Y, Shono T, Kamikawa K, Urata A, Nasu J, Imamura H, Matsushita I, Kakuma T, Tada S. Endoscopic retrograde cholangiopancreatography-related complications for bile duct stones in asymptomatic and symptomatic patients. *JGH Open*. 2021 Dec 2; 5(12): 1382-1390. <https://doi.org/10.1002/jgh3.12685> PMID: 34950782; PMCID: PMC8674545.
- [13] Xu XD, Qian JQ, Dai JJ, Sun ZX. Endoscopic treatment for choledocholithiasis in asymptomatic patients. *J Gastroenterol Hepatol*. 2020; 35(1): 165-169. <https://doi.org/10.1111/jgh.14790>
- [14] Hakuta R, Hamada T, Nakai Y, et al. Natural history of asymptomatic bile duct stones and association of endoscopic treatment with clinical outcomes. *J Gastroenterol*. 2020; 55(1): 78-85. <https://doi.org/10.1007/s00535-019-01612-7>
- [15] Attili AF, De Santis A, Capri R, Repice AM, Maselli S. The natural history of gallstones: the GREPCO experience. The GREPCO Group. *Hepatology*. 1995; 21(3): 655-660. <https://doi.org/10.1002/hep.1840210309>
- [16] Sayin SI, Wahlström A, Felin J, et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tau-ro-beta-muricholic acid, a naturally occurring FXR antagonist. *Cell Metab*. 2013; 17(2): 225-235. <https://doi.org/10.1016/j.cmet.2013.01.003>
- [17] Lemoine S, Marteau P. Gut microbial profile in primary biliary cholangitis: Towards bioindicators. *Clin Res Hepatol Gastroenterol*. 2017; 41(5): 507-508. <https://doi.org/10.1016/j.clinre.2017.06.002>
- [18] Song ST, Cai LY, Zeng X, Xie WF. Gut Microbial Profile in Asymptomatic Gallstones. *Front Microbiol*. 2022 Jun 13; 13: 882265. <https://doi.org/10.3389/fmicb.2022.882265> PMID: 35770155; PMCID: PMC9234526.
- [19] Fändriks L. Roles of the gut in the metabolic syndrome: an overview. *J Intern Med*. 2017; 281(4): 319-336. <https://doi.org/10.1111/joim.12584>
- [20] Song ST, Shi J, Wang XH, et al. Prevalence and risk factors for gallstone disease: A population-based cross-sectional study. *J Dig Dis*. 2020; 21(4): 237-245. <https://doi.org/10.1111/1751-2980.12857>
- [21] Wang Q, Hao C, Yao W, Zhu D, Lu H, Li L, Ma B, Sun B, Xue D, Zhang W. Intestinal flora imbalance affects bile acid metabolism and is associated with gallstone formation. *BMC Gastroenterol*. 2020 Mar 6; 20(1): 59. <https://doi.org/10.1186/s12876-020-01195-1> PMID: 32143645; PMCID: PMC7060658.
- [22] Ridlon JM, Devendran S, Alves JM, Doden H, Wolf PG, Pereira GV, Ly L, Volland A, Takei H, Nittono H, Murai T, Kurosawa T, Chlipala GE, Green SJ, Hernandez AG, Fields CJ, Wright CL, Kakiyama G, Cann I, Kashyap P, McCracken V, Gaskins HR. The 'in vivo lifestyle' of bile acid 7 α -dehydroxylating bacteria: comparative genomics, metatranscriptomic, and bile acid metabolomics analysis of a defined microbial community in gnotobiotic mice. *Gut Microbes*. 2020 May 3; 11(3): 381-404. <https://doi.org/10.1080/19490976.2019.1618173> Epub 2019 Jun 9. PMID: 31177942; PMCID: PMC7524365.

- [23] Wu T, Zhang Z, Liu B, Hou D, Liang Y, Zhang J, Shi P. Gut microbiota dysbiosis and bacterial community assembly associated with cholesterol gallstones in large-scale study. *BMC Genomics*. 2013 Oct 1; 14: 669. <https://doi.org/10.1186/1471-2164-14-669> PMID: 24083370; PMCID: PMC3851472.
- [24] Shrestha R, Chayaput P, Wongkongkam K, Chanruangvanich W. Prevalence and predictors of postcholecystectomy syndrome in Nepalese patients after 1 week of laparoscopic cholecystectomy: a cross-sectional study. *Sci Rep*. 2024 Feb 28; 14(1): 4903. <https://doi.org/10.1038/s41598-024-55625-1> PMID: 38418688; PMCID: PMC10902287.
- [25] Grigorieva I. N., Scherbakova L. V. Lipid profile in gallstone disease: new perspectives. *Atheroscleroz*. 2011; 7(1): 70-75. (In Russ.)